BRIEFING BOOK

DERMATOLOGIC AND OPHTHALMIC DRUGS ADVISORY COMMITTEE MEETING

LUCENTIS® (ranibizumab injection)

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GLOSSARY OF ABBREVIATIONS

AMD	age-related macular degeneration
APTC	Antiplatelet Trialists' Collaboration
ATE	arterial thromboembolic event
BCVA	best corrected visual acuity
CFT	central foveal thickness
CSME(-CI)	clinically significant macular edema (with center involvement)
CVA	cerebrovascular accident
DME	diabetic macular edema
DR	diabetic retinopathy
DRCR.net	Diabetic Retinopathy Clinical Research Network
ETDRS	Early Treatment Diabetic Retinopathy Study
FA	fluorescein angiography
FP	fundus photography
HbA_{1c}	glycosylated hemoglobin
ICH	International Conference on Harmonisation
IOP	intraocular pressure
LOCF	last observation carried forward
MI	myocardial infarction
NEI VFQ-25	National Eye Institute Visual Functioning Questionnaire–25
OCT	optical coherence tomography
NPDR	non-proliferative diabetic retinopathy
PDR	proliferative diabetic retinopathy
PRP	panretinal photocoagulation
RIDE	Study FVF4168g
RIDE	Study FVF4170g
RVO	retinal vein occlusion
sBLA	supplemental Biologics License Application
TIA	transient ischemic attack
U.S. FDA	United States Food and Drug Administration
VA	visual acuity
VEGF	vascular endothelial growth factor

GLOSSARY OF OPHTHALMOLOGY TERMS

Age-related macular degeneration (AMD)	A medical condition that usually affects older adults resulting in a loss of vision in the center of the visual field. It is a major cause of blindness and visual impairment in adults >50 years.
Best corrected visual acuity (BCVA)	The maximum visual acuity that a patient can achieve with full correction with glasses.
Cataract	A cloudy or opaque area in the normally clear lens of the eye.
Central foveal thickness (CFT)	The thickness of the center-most part of the macula, as measured using optical coherence tomography. The fovea is responsible for the highest levels of detail in central vision.
Contrast sensitivity	A measure of the ability to distinguish between finer and finer increments of light versus dark.
Diabetic macular edema (DME)	An eye disease that results from damaged blood vessels in the eye leaking fluid into the central portion of the retina (macula). The leaking causes edema (swelling) and results in blurred vision.
Diabetic retinopathy (DR)	A condition occurring in people with diabetes, which causes progressive damage to the retina, the light-sensitive lining at the back of the eye.
ETDRS diabetic retinopathy severity score	A standardized, well-validated scoring system that is used to document the extent of damage and changes over time in a patient's diabetic retinopathy.
Fluorescein angiography (FA)	An eye test that uses a special dye and camera to look at blood flow in the retina and choroid.
Fundus photography (FP)	A photograph of the interior surface of the back of the eye, including the macula, retinal periphery, and optic disc.
Intraocular pressure (IOP)	The fluid pressure inside the eye.
Legal blindness	A level of vision loss that has been legally defined to determine eligibility for Social Security benefits in the U.S. The clinical diagnosis refers to a central visual acuity of 20/200 or less in the better eye with the best possible correction, and/or a visual field of 20 degrees or less.
Optical coherence tomography (OCT)	A noninvasive imaging tool that allows for a comprehensive cross-sectional evaluation of the macula including overall retinal thickness, the location and extent of abnormal fluid collections, the health/status of various retinal layers, and the presence of many retinal diseases.
Retinal vein occlusion (RVO)	A blockage of the small veins that carry blood away from the retina that causes painless loss of vision
Visual acuity (VA)	The clarity or sharpness of vision.

1. EXECUTIVE SUMMARY

Genentech is seeking approval of a supplemental Biologics License Application (sBLA) for Lucentis® (ranibizumab injection) to add an indication for treatment of diabetic macular edema (DME), a major cause of vision loss and blindness.

The clinical trial data demonstrate that Lucentis has a highly favorable benefit–risk profile to support its use in DME and that it could redefine the standard of care for the first time in more than 25 years by bringing an unprecedented combination of benefits to many patients. The most important of these is rapid and sustained recovery of substantial levels of lost vision.

Lucentis has received regulatory approval for the treatment of visual impairment due to DME in 69 countries as of May 2012.

Treatment in U.S. Is Limited, Medical Need Remains

Approximately 25.8 million Americans (8.3% of the population) have diabetes, which is now the leading cause of new cases of blindness among Americans aged 20–74 (CDC Diabetes Fact Sheet 2011).

Over time, diabetes damages blood vessels in the eye. When this happens, a patient is said to have diabetic retinopathy (National Eye Institute 2012). These damaged blood vessels can leak blood and fluid into the central portion of the retina, called the macula, which is responsible for sharp, central vision (National Eye Institute 2012). The leaking causes swelling and blurred vision—the condition known as diabetic macular edema (National Eye Institute 2012).

The 2005–2008 National Health and Nutrition Examination Survey (NHANES) conducted by the National Center for Health Statistics estimates that among Americans aged 40 years and older, more than 4.2 million have diabetic retinopathy (Zhang et al. 2010). A subsequent analysis estimates that 560,500 have DME (Bressler et al. 2012), a complication for which there are currently no FDA-approved medicines.

Impaired vision can have an impact on the ability to work and do everyday tasks such as reading and driving, which can stifle independence and negatively affect quality of life.

The current standard of care for DME is laser surgery, which is used to treat a number of retinal conditions (National Eye Institute 2012). The technique has been shown to slow the rate of vision loss and stabilize vision but has demonstrated only limited ability to restore lost vision (ETDRS Research Group 1985). In addition, the therapeutic effects have a slow onset, and treatment complications can negatively affect eye health and vision (ETDRS Research Group 1985). For example, irreversible blind spots known as scotomas and decreased contrast and color sensitivity are well-recognized complications of macular laser surgery. In addition, inadvertent placement of laser burns

in or too close to the center of the macula can cause irreversible and immediate loss of central vision (Writing Committee for DRCR.net 2007).

Therapy with Lucentis Could Redefine Standard of Care

Lucentis inhibits vascular endothelial growth factor (VEGF-A), a protein that plays a critical role both in the formation of new blood vessels and in the hyperpermeability (leakiness) of blood vessels. Lucentis, which is administered by periodic injections into the eye, was approved by the FDA for treatment of wet age-related macular degeneration (AMD) in 2006 and for macular edema following retinal vein occlusion (RVO) in 2010.

The sBLA for DME is based on results from the RIDE and RISE studies, two identically designed, double-masked, sham treatment–controlled Phase III clinical trials, which showed that people with DME who received treatment with Lucentis had significant benefits compared with patients in the control group including rapid and sustained improvements in visual acuity, a reduced likelihood of significant vision loss, and reductions in the severity and progression of their underlying diabetic retinopathy. A majority of patients who received Lucentis achieved 20/40 vision (the level needed to read typical newsprint or obtain a driver's license (CDC Vision Health Initiative 2009) and many reported improvements in quality of life measures.

RIDE and RISE Efficacy Overview

The multicenter, parallel studies included 759 patients randomized into three groups to receive monthly treatment by 0.3-mg Lucentis injection, 0.5-mg Lucentis injection, or sham injections (control group) in one treatment eye. Primary outcomes were evaluated at 24 months and have been published in the journal *Ophthalmology* (Nguyen et al. 2012). After 24 months, patients from the control group were able to cross over to receive treatment with 0.5 mg Lucentis, and all patients were followed for 36 months. Pooled 24-month results showed the following benefits:

1. Significant, rapid, and sustained improvements in vision with Lucentis treatment compared with the control group including:
    - A significantly greater number of patients who received Lucentis were able to read at least 15 more letters (three lines) on the eye chart than they could at the start of the study: 39.2%, 42.5%, and 15.2% for the 0.3-mg, 0.5-mg, and control groups, respectively (primary endpoint).
    - Patients who received Lucentis had significantly greater average gains in eye chart reading scores from the start of the study: an average of 11.7 letters, 12 letters, and 2.5 letters for the 0.3-mg, 0.5-mg, and control groups, respectively. Average gains for patients in both Lucentis groups were equal to more than two lines on the eye chart. The differences were statistically significant starting at Day 7 and at each subsequent monthly timepoint.

- A significantly greater number of patients receiving Lucentis reached vision of 20/40 (on the Snellen scale): 57.2%, 62.7%, and 36.2% for the 0.3-mg, 0.5-mg, and control groups, respectively.
- Significantly fewer patients treated with Lucentis experienced substantial loss of vision (15 letters or more): 2.0%, 3.2%, and 9.3% for the 0.3-mg, 0.5-mg, and control groups, respectively.

2. Significant improvements in retinal anatomy in patients who received Lucentis compared with the control group including:
   - Patients who received Lucentis had a rapid and significantly greater average reduction in retinal swelling (central foveal thickness).
   - A significantly greater proportion of patients had resolution of retinal vascular leakage.
3. Significant impact on severity and progression of the underlying diabetic retinopathy disease in patients who received Lucentis including:
   - A significantly greater proportion of patients receiving Lucentis experienced an improvement in the severity of their diabetic retinopathy compared with the control group.
   - Significantly fewer patients receiving Lucentis had worsening of diabetic retinopathy severity.
   - Significantly fewer patients receiving Lucentis developed proliferative (advanced) diabetic retinopathy and/or its complications (post hoc analysis).
4. Improvements in quality of life measures in patients who received Lucentis:
   - Consistent trends showing better improvements in overall visual function and vision-related quality of life measured by the National Eye Institute Visual Functioning Questionnaire-25 (NEI VFQ-25) provide additional supportive evidence of benefit in Lucentis-treated patients.

All of the above benefits observed in Lucentis-treated patients at 24 months were also maintained at Month 36. The efficacy findings were consistently replicated in both studies.

RIDE and RISE Safety Overview

The safety of Lucentis in DME was investigated in the context of a well-established safety profile. More than 10,000 patients worldwide have received Lucentis for a number of eye conditions in investigational clinical trials sponsored by Genentech or Novartis. Patient exposure in clinical practice is estimated to exceed 1.2 million treatment-years since initial approval in 2006, and the safety profile of Lucentis has not changed substantially since then. The safety analysis of Lucentis in the DME population therefore primarily sought to identify whether unexpected, more severe, or more frequent safety events occurred.

In RIDE and RISE, Lucentis was generally well-tolerated in patients with DME through 36 months, with a safety profile similar to that established in patients with wet AMD and

RVO. Treatment with Lucentis was associated with overall low rates of adverse events across all groups.

Primary safety analyses were completed at 24 months and pooled results showed that the incidence of ocular and non-ocular adverse events was generally similar among the three treatment groups, as described below:

- The rates of ocular serious adverse events (SAEs) occurring in the study eye in patients receiving Lucentis at either dose were low (generally $<0.05\%$ per injection), primarily procedure-related, and consistent with the ocular safety profile established for intravitreal injection for other retinal diseases. The ocular risks are clearly and appropriately described in the current U.S. Product Label (Appendix 1).

- The overall rates of non-ocular AEs and SAEs potentially related to systemic VEGF inhibition were generally similar for patients receiving either dose of Lucentis compared with the control group.

  – A greater incidence of strokes was observed in patients treated with 0.5 mg Lucentis compared with the control group, but not in patients treated with 0.3 mg Lucentis: 3 (1.2%), 8 (3.2%), and 4 (1.6%) patients for the 0.3-mg, 0.5-mg, and control groups, respectively. Although uncommon, trends toward increased incidence of arteriothromboembolic events (ATEs), which include stroke events, have also been observed in some prior studies of Lucentis in other diseases. The current Lucentis label includes a warning regarding the potential risk of ATEs following intravitreal use of VEGF inhibitors. Genentech has proposed revised wording for the U.S. Product Label to include observed rates of ATEs, including stroke, in RIDE and RISE (Appendix 2).

  – A greater incidence of deaths from any cause was observed in patients treated with Lucentis: 7 (2.8%), 11 (4.4%), and 3 (1.2%) for 0.3-mg, 0.5-mg, and control groups, respectively. Although causes of death were those typical of patients with advanced diabetic complications, a potential relationship between these events and intravitreal use of VEGF inhibitors cannot be excluded. These events are addressed in the proposed U.S. Product Label for Lucentis in DME (Appendix 2).

  – A greater incidence of SAEs of hypertension (grouped terms) was observed in patients treated with Lucentis, with more such events in the 0.5-mg group than the 0.3-mg group: 3 (1.2%), 6 (2.4%), and 1 (0.4%) for the 0.3-mg, 0.5-mg, and control groups, respectively. The overall incidence of AEs of hypertension (grouped terms) was numerically higher in the 0.5-mg group: 48 (19.2%), 56 (22.4%), and 51 (20.4%) for the 0.3-mg, 0.5-mg, and control groups, respectively. The trend toward a dose-dependent increase in hypertension SAEs, the trend toward a higher rate of hypertension AEs in the 0.5-mg group, and the biologic plausibility of VEGF inhibition causality for hypertension suggest

that a potential risk of increased hypertension rates with Lucentis treatment cannot be excluded.

- A greater incidence of wound healing complications was observed in patients treated with Lucentis: 2 (0.8%), 6 (2.4%), and 0 (0%) for the 0.3-mg, 0.5-mg, and control groups, respectively. The trend toward a dose-dependent increase in wound healing AEs and the biologic plausibility of VEGF inhibition causality suggest that a potential risk of impaired wound healing with Lucentis treatment cannot be excluded.

Dosing

In patients with DME, both doses of Lucentis were similarly efficacious and superior to sham treatment, with visual and anatomic improvements maintained through 24 and 36 months. Overall, the 0.3-mg and 0.5-mg doses of Lucentis were well tolerated.

Genentech has considered the totality of the clinical trial data to arrive at a dosing recommendation for Lucentis in DME: RIDE and RISE demonstrate clearly superior, similar efficacy for both doses of Lucentis compared with control at 24 and 36 months. However, there was no evidence of incremental benefit with the higher 0.5-mg dose at 36 months. In addition, although the number of events are low, a dose-dependent safety differential between the 0.3-mg and 0.5-mg doses cannot be excluded for certain adverse events. In aggregate, these data suggest that the optimal dose for Lucentis in DME is 0.3 mg monthly.

Summary, Benefit–Risk Evidence Supports Lucentis Treatment for DME

The totality of evidence supports the use of Lucentis in treatment of DME. As the first FDA-approved medical treatment, Lucentis could provide many of the estimated half a million Americans suffering from DME with the opportunity to regain substantial amounts of lost vision—and with it, the ability to engage in everyday activities like reading and driving.

The approval of Lucentis would redefine the current standard of care for DME, which as of now primarily serves to slow, not reverse the progression of vision loss, and which has not advanced in more than 25 years.

The findings of the RISE and RIDE trials clearly demonstrate clinically significant benefits for patients receiving Lucentis, including rapid and sustained improvements in visual acuity and retinal anatomy, reduced rates of significant vision loss, and improvements in the severity and progression of the underlying diabetic retinopathy disease. Most patients treated with Lucentis reached vision of 20/40 or greater, the level needed to read typical newsprint or obtain a driver's license in most U.S. states. Improvements observed at 24 months were maintained at 36 months.

Lucentis was generally well-tolerated in patients with DME with relatively small differences in safety event rates between treatment and control groups.

The evidence indicates that the benefits largely outweigh the risks in use of Lucentis to treat patients with DME and that Lucentis warrants FDA approval in DME at the recommended 0.3-mg dose.

2. FDA ADVISORY COMMITTEE MEETING: 26 JULY 2012

This briefing document presents an overview of the efficacy and safety data from the Study FVF4168g (hereinafter "RIDE") and Study FVF4170g (hereinafter "RISE") of ranibizumab in patients with diabetic macular edema (DME). This information is intended to inform discussion by the Dermatologic and Ophthalmic Drugs Advisory Committee Meeting of 26 July 2012 regarding Genentech's pending supplemental Biologics License Application for ranibizumab injection (Lucentis®) for treatment of DME.

2.1 INTRODUCTION

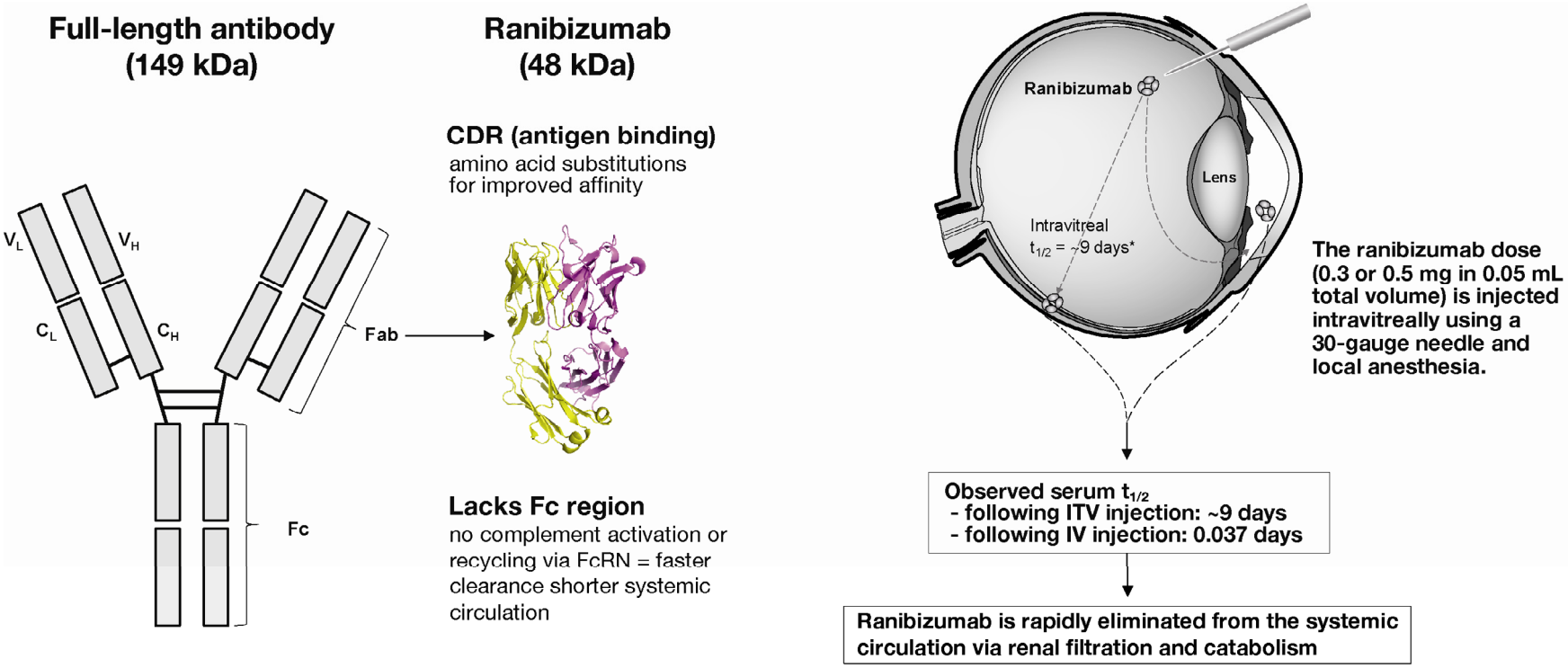
Ranibizumab is a recombinant, affinity matured, humanized immunoglobulin G1 (IgG1) kappa isotype monoclonal antibody fragment, which is designed for intraocular use. In contrast to a full-length antibody, this fragment known as a "Fab" lacks an Fc region, and is therefore smaller at approximately one-third the molecular weight. Ranibizumab was designed specifically as a Fab to achieve better penetration of the retina following intravitreal injection, less inflammation via Fc-complement engagement, and rapid clearance once the molecule exits the eye and enters the systemic circulation. These design elements were intended to maximize potential efficacy while limiting undesired systemic effects (Figure 1).

Ranibizumab binds to and inhibits the biologic activity of human vascular endothelial growth factor A (VEGF-A). The binding of ranibizumab to VEGF-A prevents the interaction of VEGF-A with its receptors (VEGFR1 and VEGFR2) on the surface of endothelial cells, reducing endothelial cell proliferation, vascular leakage, and new blood vessel formation.

Ranibizumab is marketed as LUCENTIS® (ranibizumab injection). The 0.5-mg dose (0.05 mL of 10 mg/mL ranibizumab solution) was approved by the U.S. Food and Drug Administration (FDA) on 30 June 2006 for the treatment of neovascular (wet) age-related macular degeneration (AMD) and on 22 June 2010 for macular edema following retinal vein occlusion (RVO) (see Lucentis® U.S. Product Label in Appendix 1).

As of 31 May 2012, ranibizumab has received regulatory approval for the treatment of neovascular AMD in 102 countries, for the treatment of visual impairment due to diabetic macular edema (DME) in 69 countries, and for the treatment of visual impairment due to retinal vein occlusion (RVO) in 67 countries. Ranibizumab has been studied in more than 10,000 patients in investigational clinical trials sponsored by Genentech or Novartis Pharma AG, Genentech's development and marketing partner for ranibizumab outside the U.S. Patient exposure in clinical practice is estimated to exceed 1.2 million patient treatment-years since initial approval in 2006.

Figure 1 Molecular Characteristics and Intravitreal Administration of Ranibizumab



C=constant region; CDR=complementarity-determining regions; Fab=antigen binding fragment; Fc=fragment crystallizable region; FcRn=the neonatal Fc receptor; H=heavy chain; ITV=intravitreal; IV=intravenous; kDa=kilodalton; L=light chain; $t_{1/2}$=half-life; V= variable region.

2.2 PROPOSED INDICATION

Ranibizumab is indicated for the treatment of patients with diabetic macular edema (DME).

2.3 DOSAGE AND ADMINISTRATION

The recommended dose of ranibizumab for the treatment of DME is 0.3 mg administered monthly as an intravitreal injection.

3. UNMET MEDICAL NEED

3.1 DIABETIC EYE DISEASE

Currently 25.8 million Americans (8.3% of the U.S. population) have diabetes, according to the Centers for Disease Control and Prevention, and it is the leading cause of new cases of blindness among American adults (CDC Diabetes Fact Sheet 2011). The 2005–2008 National Health and Nutrition Examination Survey (NHANES) conducted by the National Center for Health Statistics estimates that more than 4.2 million Americans aged 40 years and older have diabetic retinopathy (Zhang et al. 2010). Vision loss from diabetic retinopathy is thus a major public health concern and is associated with considerable socioeconomic and quality of life effects (Javitt et al. 1994).

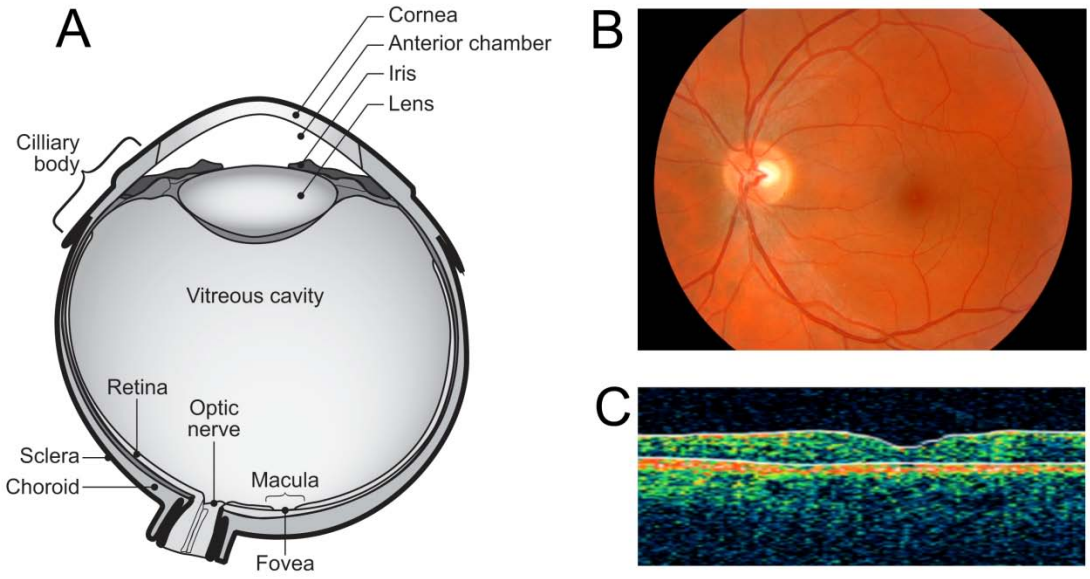
Diabetic macular edema (DME), swelling of the central retina associated with vision loss, is an advanced complication of diabetic retinopathy and is responsible for much of the visual impairment resulting from diabetes (Johnson et al. 2009). The 2005–2008 NHANES study estimates that 560,500 Americans aged 40 years and older have DME (Bressler et al. 2012). Adequate glucose management through the use of both oral hypoglycemic agents and insulin is a mainstay of diabetes therapy, and prevention and diminution of long-term diabetic complications can be achieved with tight glucose control. For example in the Diabetes Control and Complications Trial, the risk of retinopathy decreased by 39% with a 10% decrease in baseline glycosylated hemoglobin (HbA_{1c}; Writing Team for the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Research Group 2002). While glycemic control is improving among Americans diagnosed with diabetes, more than 40% of patients still do not reach the recommended glycemic target (Cheung et al. 2009). Consequently, despite best efforts at tight metabolic control, a significant number of Americans will develop diabetic retinopathy and DME over time.

Currently available therapies for diabetic retinopathy have shown limited ability to provide meaningful increases in vision and do not modify the underlying disease process or halt disease progression. A treatment that might slow the progression of the disease and substantially improve visual function would represent a major advance and help patients with diabetic retinopathy to remain independent and productive.

3.1.1 Diabetic Retinopathy–Retinal Anatomy and Disease State

The retina is the light-sensitive nerve tissue that lines the back of the eye. It consists of the peripheral retina, which provides peripheral (side) and night vision, and the central retina or macula, which provides fine detail and color vision. Near the center of the macula region is the fovea, which is responsible for the sharpest central vision essential for reading, watching television, driving, and any activity where visual detail is of primary importance. Figure 2 shows a schematic of the normal retinal anatomy, a fundus photograph (a photograph of the interior surface of the back of the eye) of a healthy retina, and an optical coherence tomography (OCT) scan showing normal retinal architecture.

Figure 2 Normal Retinal Anatomy

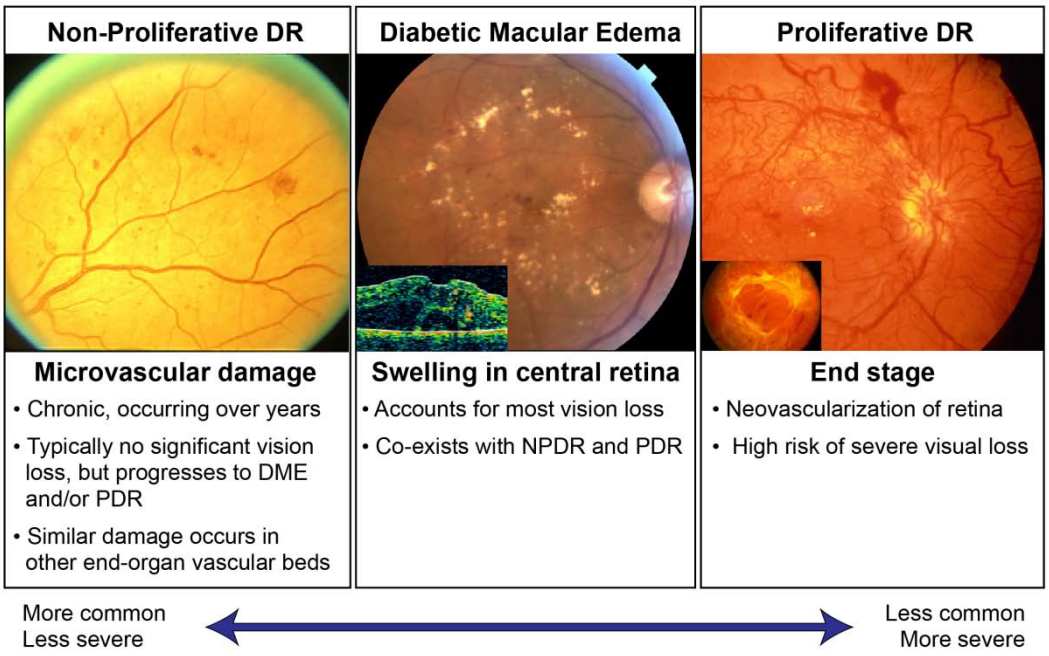


(A) a schematic of the anatomy of the eye; (B) a color fundus photograph of a normal retina; (C) an optical coherence tomography (OCT) scan of normal retinal architecture and thickness.

Diabetes causes a spectrum of retinal disease, which can be diagnosed on clinical examination through a dilated pupil. Regular screening examinations are recommended on at least an annual basis so that accurate diagnosis, staging, and appropriate treatment may occur. Risk factors that increase the likelihood of developing diabetic retinopathy and DME include duration of diabetes of more than 10 years and elevated HbA_{1c} level (Zhang et al. 2010).

Three forms of retinopathy are commonly recognized in association with diabetes (Figure 3): non-proliferative diabetic retinopathy (NPDR); diabetic macular edema (DME); and proliferative diabetic retinopathy (PDR).

Figure 3 Classification of Diabetic Retinopathy

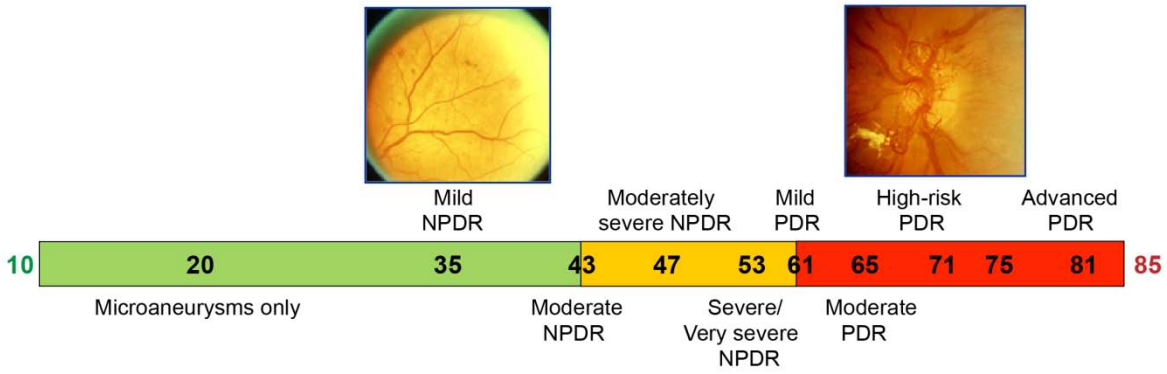


DR = diabetic retinopathy.

Source: The NPDR and PDR images are courtesy of the Fundus Photograph Reading Center, Dept. of Ophthalmology & Visual Sciences, University of Wisconsin—Madison. Collection of Diabetic Grading Standards available at: http://eyephoto.ophth.wisc.edu/ResearchAreas/Diabetes/DiabStds.htm.

NPDR may range from mild to severe, and over time it may progress to the more severe PDR, which manifests as new blood vessel growth (or neovascularization) on the surface of the retina, optic nerve, or iris (Figure 4). PDR is associated with a high risk of visual loss, as these new blood vessels are fragile and may break and bleed into the vitreous cavity of the eye. Severe vision loss can result from vitreous hemorrhage, retinal detachment, and neovascular glaucoma (an eye disease in which the optic nerve is damaged) (Diabetic Retinopathy Study Research Group 1979). Diabetic macular edema (DME) coexists with either NPDR or PDR. Of all of the diabetic retinopathy subtypes, DME accounts for the majority of vision loss associated with diabetes.

Figure 4 Diabetic Retinopathy Severity Level

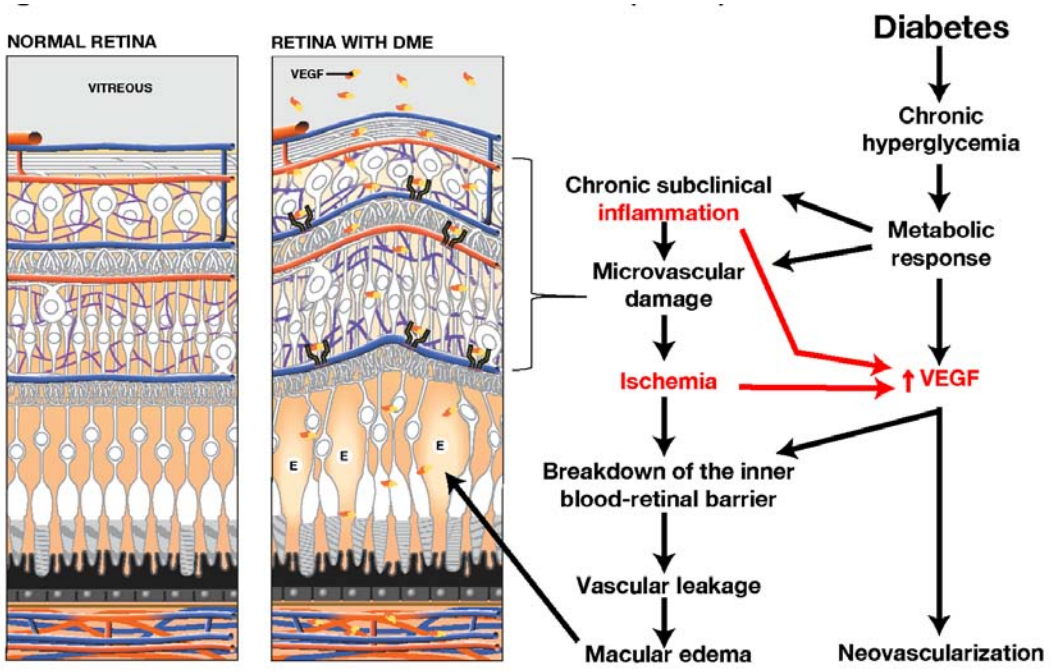


Images courtesy of the Early Treatment Diabetic Retinopathy Study Research Group.

Diabetic retinopathy progresses (worsens) in discrete levels that can be described on color fundus photographs using the ETDRS diabetic retinopathy severity scale (ETDRS Research Group 1991).

DME arises from the breakdown of the blood retinal barrier, resulting in the accumulation of fluid, lipid, and protein in the retina (Figure 5). Breakdown of the blood retinal barrier and subsequent leakage in DME may occur in two patterns—focal or diffuse (Bresnick 1986). In the first, focal leakage may arise from microaneurysms (focal dilation of the venous end of retinal capillaries). In the second, diffuse leakage occurs through the walls of chronically damaged capillaries. Many patients with DME have a combination of focal and diffuse leakage, and both of these may be treated with macular laser.

Figure 5 Pathogenesis of Diabetic Macular Edema



DME = diabetic macular edema; E = edema; VEGF = vascular endothelial growth factor. In DME, chronic hyperglycemia leads to microvascular damage, which in turn causes ischemia and upregulation of VEGF. This results in the breakdown of the blood-retinal barrier, causing vascular leakage and macular edema.

DME that either directly involves the fovea, or is at high risk for doing so, is referred to as "clinically significant macular edema" (CSME) (ETDRS Research Group 1985). When the center of the fovea is involved by CSME, the DME is defined as CSME with center involvement (CSME-CI), as opposed to "CSME without center involvement" (ETDRS Research Group 1987). Patients with CSME-CI either are already visually impaired or are at high risk of developing vision loss (ETDRS Research Group 1985).

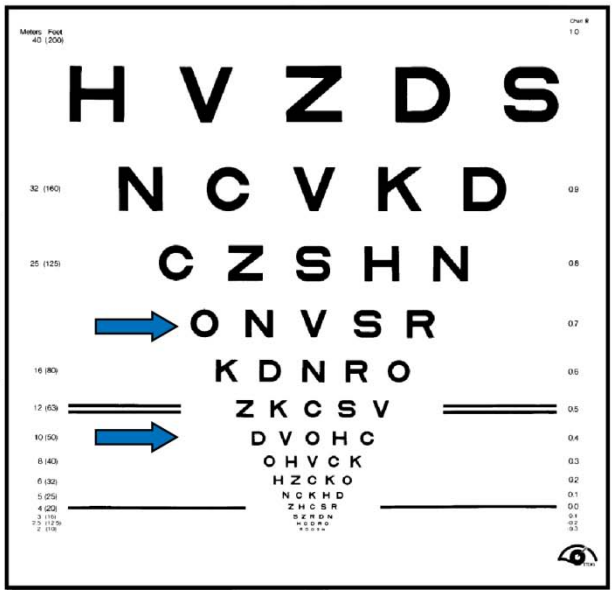
The ETDRS Research Group also established the ETDRS visual acuity chart, which has become the standardized outcome measure in ophthalmology clinical trials and allows the reproducible measurement of vision in patients across different clinical trial centers (Figure 6). It yields a measurement known as best corrected visual acuity (BCVA), which is the maximum visual acuity that a patient can achieve with full correction with glasses. It is measured as the number of standardized chart letters read by the patient.

Figure 6 ETDRS Standardized Eye Chart for Clinical Trials

Logarithmic, standardized eye chart improves statistical comparisons for ophthalmology clinical trials

More letters read = better visual acuity (VA)

Delta of:
15 letters = 3 lines
10 letters = 2 lines
5 letters = 1 line



The arrows represent a delta (change) of 15 letters or 3 lines on the ETDRS chart. A standard primary endpoint in clinical trials is the proportion of patients gaining ≥15 letters.

3.1.2 Current Treatment and Unmet Medical Need

3.1.2.1 Macular Laser

There is no FDA-approved medical therapy for DME. Macular laser treatment constitutes the current standard of care, and its efficacy and safety profile has not changed since 1985, when the ETDRS study demonstrated its beneficial effect in preventing vision loss in patients with defined CSME. Laser treatment is recommended when CSME is present, even for patients with 20/20 vision, to address the high likelihood of associated progression to vision loss. The goal of laser therapy timing is to intervene before vision loss, with the benefit of preventing visual decline demonstrated to outweigh the risks of the laser procedure.

Although macular laser treatment does reduce the incidence of moderate vision loss, in both the ETDRS and in recent studies relatively few patients with vision loss due to DME experienced significant improvements in BCVA after laser treatment, and any improvement tended to occur slowly (ETDRS Research Group 1985; DRCR.net 2008, 2010; Mitchell et al. 2011).

Although typically performed as an office-based procedure, macular laser treatment is not without risks, owing to its tissue-destructive nature. As a result, the eye anatomy is altered and irreversible blind spots known as scotomas form. Decreased contrast and color sensitivity, and progressive atrophy of the retinal pigment epithelium are well-recognized complications. These can develop either immediately after treatment or over time and inadvertent placement of laser burns excessively close to or in the center of the fovea can cause irreversible and immediate loss of central vision

(Chang et al. 2007; Writing Committee for DRCR.net 2007; Bressler et al. 2009). Macular laser thus cannot be safely applied to leakage that is very close to the center of foveal vision, and therefore some types of DME are not amenable to laser treatment.

Macular laser cannot be used to treat other forms of diabetic retinopathy and does not alter the progression of NPDR to PDR over time. Because of these limitations, a treatment with rapid, durable, and more pronounced improvements in vision would be an important advance in the management of DME.

3.2 DEVELOPMENT RATIONALE FOR RANIBIZUMAB IN TREATMENT OF DME

Diabetic macular edema results from pathologically increased retinal vascular permeability (Cunha-Vaz et al. 1975). Recognition of VEGF as the primary cytokine mediating this increase (Tolentino et al. 1996; Qaum et al. 2001) and observation of increased intraocular VEGF levels in DME (Frank et al. 1996; Funatsu et al. 2002) led to the hypothesis that a VEGF-signaling blockade might be beneficial for treatment of diabetic macular edema.

The rationale for use of ranibizumab in the treatment of patients with DME is supported by several lines of evidence, including the mechanism of action, nonclinical studies in relevant animal models, and pilot clinical studies. Early-phase clinical trials demonstrated that intravitreal ranibizumab reduced macular edema and improved visual acuity in patients with DME (Chun et al. 2006; Nguyen et al. 2006).

Subsequent large Phase III and Phase III-scope studies (the Protocol I study, sponsored by the Diabetic Retinopathy Clinical Research Network [DRCR.net], and the RESTORE study, sponsored by Novartis Pharma AG, Genentech's development and marketing partner for ranibizumab outside the U.S.) provided additional supportive data on the efficacy and safety of ranibizumab in DME. Data from these trials emerged over the last 2 years, while Genentech's Phase III clinical program was still ongoing (Nguyen et al. 2009, 2010; DRCR.net 2010; Mitchell et al. 2011). These studies, although differing in duration and dose regimen from RIDE and RISE, provide additional supportive evidence of the efficacy and safety of ranibizumab in DME patients and further support Genentech's pivotal clinical trial results. The outcomes of these studies are briefly summarized here to provide context from additional published literature in this setting for the purposes of the Dermatologic and Ophthalmic Drugs Advisory Committee Meeting. Importantly, these trials were not sponsored by Genentech and were not a part of Genentech's sBLA; FDA agreed in presubmission meetings to this approach.

The Diabetic Retinopathy Clinical Research Network (DRCR.net) is a collaborative network founded in 2002 designed to facilitate multicenter clinical research of diabetic retinopathy, diabetic macular edema, and associated conditions. It includes more than 109 participating sites (offices), and is funded by the National Eye Institute (NEI). The DRCR.net Protocol I study was a randomized, multicenter clinical trial that

compared ranibizumab (0.5-mg) plus prompt or delayed focal laser, triamcinolone (intravitreal steroid) plus prompt laser, and sham injections plus prompt focal/grid laser, with a primary endpoint of mean change in BCVA after 12 months (DRCR.net 2010). Ranibizumab dosing was on an as-needed basis (at most monthly) according to protocol-specified criteria of vision and OCT characteristics. There were 691 patients (854 eyes) with DME enrolled in this study; baseline characteristics were similar to those of patients in RIDE and RISE. This cohort has now been followed to 2 years and data on efficacy, safety, and dosing regimen are available (Elman et al. 2011).

At the 1-year timepoint, the mean change in BCVA from baseline in both ranibizumab groups was 9 ETDRS letters, which was significantly greater than in the sham plus laser group (+3 letters; differences in mean change in BCVA [95% CI] were 5.8 letters [3.2 to 8.5] and 6.0 letters [3.4 to 8.6] for the ranibizumab plus prompt laster group and ranibizumab plus deferred laser group, respectively). The triamcinolone plus prompt laser group gained 4 letters (not statistically different than sham plus prompt laser). Results show that 28%–30% of the ranibizumab-treated patients gained ≥15 ETDRS letters from baseline at 1 year compared with 15% of sham plus prompt laser–treated patients (DRCR.net 2010). These results were generally consistent with patients who had completed 2 years of follow-up (Elman et al. 2011), although the treatment algorithm in the second year allowed for less than monthly dosing, and the median number of injections was 2–3.

Ranibizumab was generally well tolerated in the DRCR.net Protocol I study. Of 375 ranibizumab-treated eyes, 1 experienced progression of a traction retinal detachment, and 3 eyes developed endophthalmitis. Elevated intraocular pressure and cataract surgery occurred more frequently in the triamcinolone-treated group (DRCR.net 2010). The safety profile at 2 years was generally consistent with the 1 year data (Elman et al 2011). No systemic events were reported attributable to study treatment, with the sham group experiencing higher rates of certain systemic events than the ranibizumab groups. The DRCR.net Protocol I study is continuing in a follow-up phase to ascertain longer-term (3-year) treatment and safety outcomes.

The RESTORE study (Mitchell et al. 2011) was a randomized, double-masked, multicenter, laser-controlled Phase III study of patients with visual impairment due to DME, conducted outside of the United States by Novartis. A total of 345 patients were enrolled. The primary objective was to demonstrate superiority of either 1) 0.5 mg ranibizumab monotherapy dosed monthly for 3 months and then on an as-needed basis per protocol-specified criteria or 2) 0.5 mg ranibizumab as an adjunct to laser treatment, compared with laser monotherapy. The primary outcome measure was the mean average change in BCVA from baseline to Month 1 through Month 12.

The RESTORE study results demonstrated that ranibizumab (both with and without laser) provided superior benefits in BCVA improvement compared with laser alone at Month 12. Improved vision of ≥10 letters was achieved by 37%–43% of ranibizumab-treated

patients compared with 16% treated with standard laser therapy alone. Ranibizumab given alone or as an adjunct to laser resulted in rapid improvements in BCVA that were sustained over 12 months of treatment, with a mean of 6.8 to 7 injections. The mean average change in BCVA was 5.9–6.1 letters in the ranibizumab groups compared with 0.8 letters with laser alone.

Ranibizumab was well tolerated; there were no cases of endophthalmitis, and there was a low rate (<1%) of increased intaocular pressure (IOP). Systemic safety demonstrated a low rate of hypertension (5.0%–8.2%) and arteriothromboembolic events (ATEs) (2.7%–3.5%) in all treatment groups without meaningful differences in the number of such events between the ranibizumab and laser control groups. The RESTORE study served as the primary basis for regulatory approvals of ranibizumab for DME outside of the U.S.

4. REGULATORY HISTORY

Following the initial U.S. regulatory approval for ranibizumab for the treatment of neovascular AMD in 2006, Genentech received advice from the FDA on a pivotal clinical trial program in DME, leading to the design and initiation of Genentech's RIDE and RISE studies.

In accordance with the FDA's advice for clinical development in DME, Genentech conducted two identical confirmatory pivotal trials in DME, each of 36 months duration, followed by an open-label extension stage. The primary endpoint (percentage of patients gaining 15 ETDRS letters in BCVA score) is an accepted, approvable, primary endpoint to demonstrate clinically significant improvement in visual function. The selection of endpoints, analysis plan, and study data presented in this briefing book allow for an assessment of effectiveness in DME in a manner generally consistent with FDA's formal advice to Genentech and its public recommendations described in the 2006 NEI/FDA Ophthalmic Clinical Trial Design and Endpoints Symposium (Csaky et el. 2008). According to the FDA, clinical effectiveness in diabetic retinopathy may be demonstrated in three ways:

1. Statistically and clinically relevant differences in visual function at 36 months or longer OR
2. Statistically significant difference in the percentage of patients at 36 months with a $\geq$3-step change on the ETDRS retinopathy scale OR
3. Both of the following:
    a) Statistically and clinically relevant differences in visual function at 24 months or longer AND
    b) "Numerically non-inferior" differences at 24 months or longer, with use of the 18-month timepoint as a baseline. (This assessment was intended to assure that benefits were likely to be maintained relative to comparator beyond 24 months.)

Consistent with the third option, Genentech designed its DME program to enable a supplemental Biologics License Application (sBLA) submission based on submission of 24-month data from RIDE and RISE.

Genentech believed that the totality of the 24-month RIDE and RISE data provided substantial evidence of the safety and efficacy of ranibizumab for the treatment of DME, and submitted its sBLA based on these data on 10 October 2011. With this initial submission, Genentech recommended that both the 0.3-mg and 0.5-mg doses be approved for the DME indication. Both doses were highly effective, with limited evidence of a dose response among key efficacy outcomes, and they exhibited a safety profile generally similar to that observed in the other approved indications. Because the Month 24 safety data in these DME studies suggested the possibility of increased risks with the 0.5-mg dose, including increased risk of stroke and death, Genentech recommended

0.3 mg as the starting dose for all DME patients and that the 0.5-mg dose be contraindicated in DME patients thought to be at particular risk of stroke and/or death.

When the 36-month RIDE and RISE safety and efficacy data became available in early 2012, the key 36-month data were submitted to FDA on 27 April 2012 to further support FDA's evaluation of ranibizumab for treatment of DME. This report of the 36-month data provided further evidence regarding the durability of benefit observed with ranibizumab, information regarding the relative safety of both doses at 36 months, and revised product labeling (Appendix 2). The revised product labeling limited the recommended dose solely to the 0.3-mg dose owing to a reevaluation of the cumulative efficacy and safety data for both doses (see Section 10.2.2 Dose Selection).

5. CLINICAL DEVELOPMENT PROGRAM

5.1 STUDY DESIGN

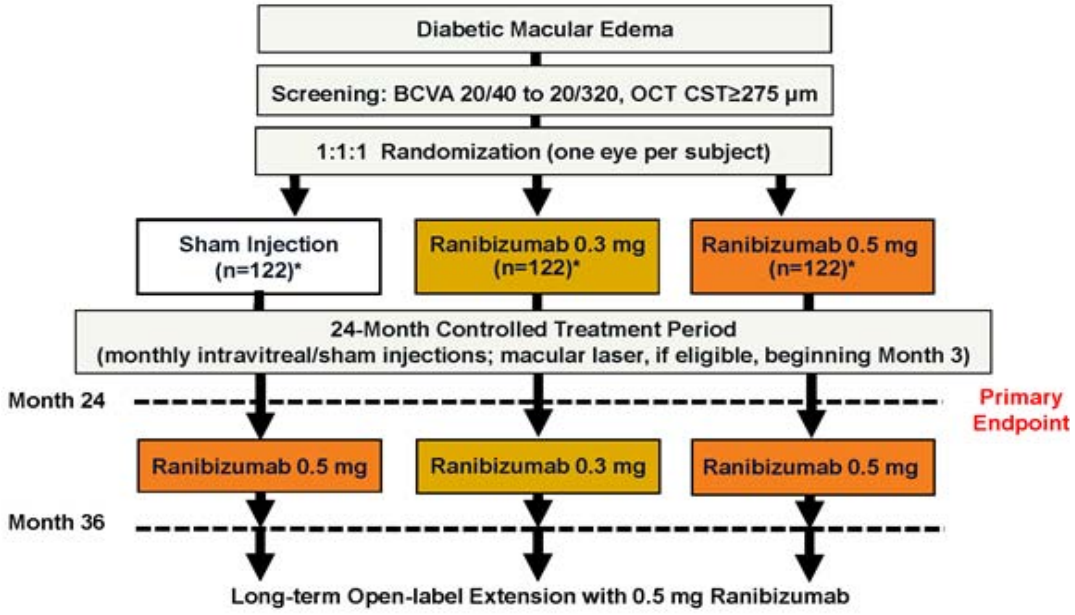
The two pivotal Phase III studies, RIDE and RISE, were multicenter, double-masked, randomized, sham injection–controlled studies to evaluate the efficacy and safety of ranibizumab injection in patients with diabetes experiencing vision loss due to clinically significant edema accumulated in the retina involving the center of the fovea (CSME-CI) secondary to diabetes mellitus.

RIDE and RISE were identical in their design, population studied, treatment regimens, study assessments, endpoints, and statistical analysis methods (Figure 7). Both studies are being conducted mainly in the United States, with a few sites in Latin America, and are ongoing.

A total of 759 patients (382 in RIDE and 377 in RISE) were randomly assigned to receive monthly 0.3 mg ranibizumab intravitreal injections, 0.5 mg ranibizumab intravitreal injections, or sham intravitreal injection, in which the eye was anesthetized and prepared for injection, and then a mock injection procedure was performed without an actual intravitreal injection. Because the “injecting” physician performing the sham or actual intravitreal injection procedure would not be masked to whether a patient was assigned to the sham or ranibizumab groups, an additional “evaluating” physician fully masked to treatment assignment was used to perform all study assessments, examinations, and evaluations.

In addition to receiving sham or intravitreal ranibizumab injections, beginning at Month 3, all patients were evaluated monthly for the need to receive standard-care macular laser. The protocol provided specific objective and subjective criteria according to which macular laser was to be administered. This was to ensure that all patients, regardless of treatment group, would receive standard-care treatment in the event that their macular edema did not respond to study treatment.

Figure 7 Overview of Study Design for RIDE and RISE



* Target enrollment per arm per study

The first 24 months of this 36-month period were sham-controlled. After Month 24, patients in the sham group who had not discontinued from study treatment could optionally cross over to receive monthly injections of 0.5 mg ranibizumab. Therefore, the sham group is labeled as "sham/0.5-mg" for the Month 36 analysis. Following protocol amendments 3 and 4 (dated 17 September 2009 and 1 June 2010, respectively), 5 sham patients with ongoing, persistent vision loss crossed over early to ranibizumab treatment at Month 23. The treatment allocation was still masked after Month 24 after all eligible patients had crossed over. However, all patients originally randomized to ranibizumab treatment continued to receive ranibizumab at the original allocated treatment dose (0.3 mg or 0.5 mg). Only patients originally randomized to sham had their treatment switched through an interactive voice response system (IVRS) after crossover. Patients and physicians knew that all patients could receive ranibizumab treatment after Month 24, but they did not know which dose would be administered.

After Month 36, patients in all treatment groups who completed the Month 36 visit and had not discontinued study treatment early were eligible to enter the open-label extension stage of the study and receive 0.5 mg ranibizumab on an as-needed basis for up to 24 additional months, or until 30 days after the marketing approval of ranibizumab for treatment of DME, whichever may occur first.

Only one eye of each patient was chosen as the study eye. If both eyes were eligible, the eye with the lower visual acuity assessed at screening was selected for study treatment unless, for medical reasons, the investigator deemed the other eye to be more appropriate for treatment and study. Following protocol amendments 3 and 4, at the

discretion of the evaluating physician, patients who were receiving study treatment and were diagnosed with bilateral DME could be given an injection of 0.5 mg ranibizumab in the fellow (non-study) eye, no more frequently than monthly.

The primary analyses were performed with data collected during the sham-controlled period through Month 24, and they were the basis of the sBLA submitted on 10 October 2011. Patients' 36-month data became available in early 2012; analyses were performed to examine the longer-term efficacy and safety of ranibizumab. A report containing the key 36-month analysis results and analysis datasets was submitted to the FDA on 27 April 2012. Both the 24-month and 36-month findings are provided and discussed in this briefing document.

5.2 DOSES INVESTIGATED

Patients randomized to the ranibizumab treatment arms received intravitreal injections of 0.3 mg or 0.5 mg every month for a total of 36 months. Two dose levels were evaluated to determine an optimal safe and efficacious dose. Both doses had previously been used safely in patients with AMD; 0.5 mg ranibizumab is the approved dose in both AMD as well as for macular edema due to RVO. Single and multiple dose-ranging studies (testing a range of 0.05 mg to 2 mg) in AMD have suggested that the 0.5-mg dose was well-tolerated and would yield efficacy at the top of the dose–response curve. Phase III clinical trial data evaluating the 0.3-mg and 0.5-mg doses in AMD suggested trends toward better efficacy with the 0.5-mg dose. Modeling and simulation studies for DME supported the use of 0.3 mg as a minimally effective dose in DME. Both the 0.3-mg and 0.5-mg doses were studied in a small, open-label investigator-sponsored study, and suggested a better anatomic response (on OCT) in patients with DME treated with the 0.5-mg dose compared with the 0.3-mg dose (Chun et al. 2006). On the basis of the data available at the time RIDE and RISE were designed, the 0.3-mg and 0.5-mg ranibizumab doses were selected for study.

5.3 PATIENT POPULATION

DME patients meeting the study inclusion and exclusion criteria were eligible for participation in RIDE and RISE; key inclusion and exclusion criteria are shown in Table 1.

Table 1 Key Inclusion and Exclusion Criteria for RIDE and RISE

Inclusion Criteria	Exclusion Criteria
• Decrease in vision determined to be primarily the result of DME • Retinal thickening on optical coherence tomography with central macular thickness ≥ 275 µm in the center subfield • Study eye BCVA score in the study eye of 20/40 to 20/320 (approximate Snellen equivalent) • Age ≥ 18 years • Signed informed consent	• History of any of the following within 3 months before the first day of the study: – Anti-angiogenic drugs in either eye – Panretinal photocoagulation, macular laser, intraocular steroids in the study eye – Cerebral vascular accident (stroke) or myocardial infarction (heart attack) – History of vitreoretinal surgery in the study eye – Active proliferative diabetic retinopathy or uncontrolled glaucoma in the study eye – Glycosylated hemoglobin (HbA_{1c}) > 12

5.4 KEY EFFICACY AND SAFETY OUTCOME MEASURES

Table 2 lists key efficacy and safety outcome measures. A full list of pre-specified endpoints and a summary of statistical considerations for RIDE and RISE is presented in Appendix 3.

Table 2 Key Efficacy and Safety Outcome Measures

Efficacy	Safety
• Visual Acuity outcomes – % Gaining ≥ 15 ETDRS letters (primary outcome) [a] – BCVA change from baseline – % Losing < 15 ETDRS letters • Contrast sensitivity • Optical coherence tomography • Macular laser • Panretinal photocoagulation laser • Diabetic retinopathy severity and progression on fundus photography • Patient-reported outcomes	• Incidence and severity of ocular adverse events • Incidence and severity of non-ocular adverse events

[a] Primary efficacy endpoint.

6. PATIENT DISPOSITION AND DEMOGRAPHICS

6.1 PATIENT DISPOSITION

A total of 759 patients—382 in RIDE and 377 in RISE—were randomly assigned to the three treatment groups in a 1:1:1 ratio in the sham, 0.3-mg, and 0.5-mg groups. Nine patients did not receive treatment; 637 (84%) patients completed the studies through Month 24, and 582 (76.7%) patients completed the study through Month 36. See Appendix 4, Table 4.1 for additional data regarding patient disposition. Figure 8 and Figure 9 present patient disposition for RIDE and RISE, respectively.

The number of patients who prematurely withdrew from study treatment and the reasons for their discontinuation were generally similar across the three groups by study, with few differences. The most common reason for discontinuation was the patient's decision.

Figure 8 Patient Disposition for RIDE

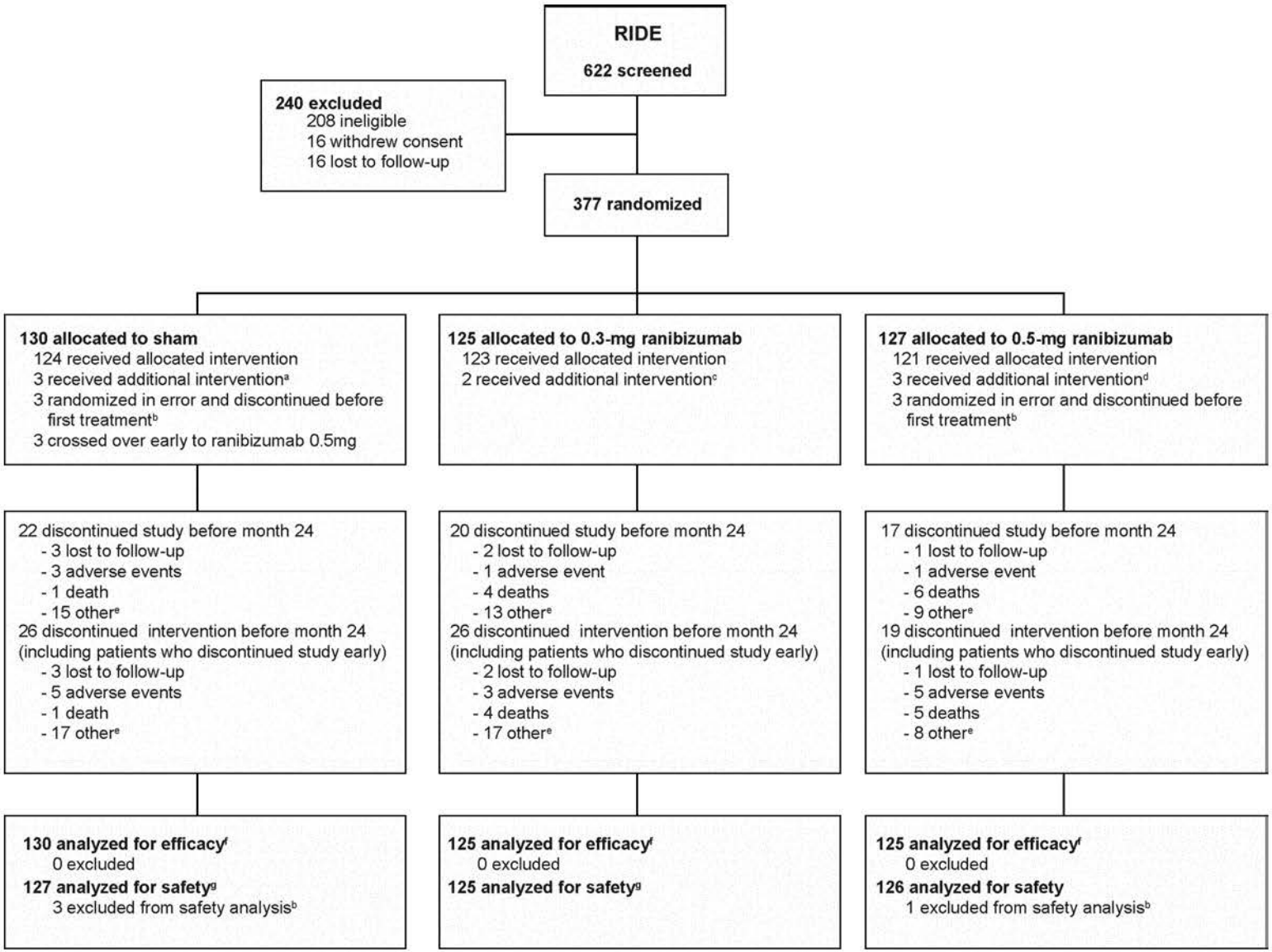


Figure 8 Patient Disposition for RIDE (cont.)

[a] Three patients received sham and 0.5 mg ranibizumab (these 3 patients crossed over early, before Month 25).

[b] Did not receive any intervention.

[c] One patient received sham and 0.3 mg ranibizumab and 1 patient received 0.3 mg and 0.5 mg ranibizumab.

[d] Two patients received sham and 0.5 mg ranibizumab and 1 patient received 0.3 mg and 0.5 mg ranibizumab.

[e] Physician's decision, patient's decision, patient noncompliance, patient's condition mandated other therapeutic intervention.

[f] Patients randomized to intervention. All efficacy analyses are intent-to-treat.

[g] The safety-evaluable population included randomized patients who received at least 1 study treatment (ranibizumab or sham injection). Treatment groups for the safety-evaluable population were defined according to the actual treatment received during the 24-month period.

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Figure 9 Patient Disposition for RISE

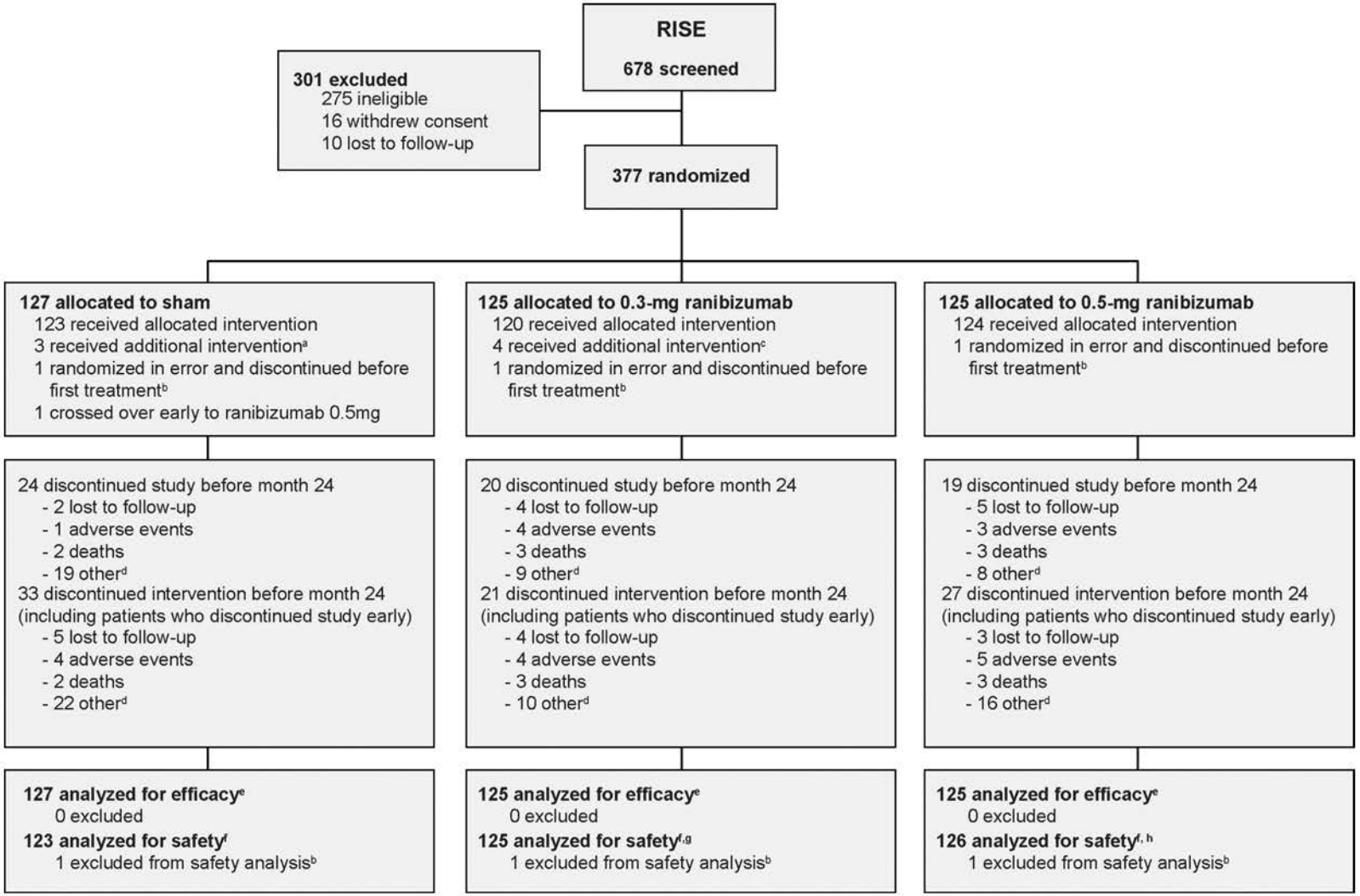

Figure 9 Patient Disposition for RISE (cont.)

[a] One patient received sham and 0.3 mg ranibizumab, 2 patients received sham and 0.5 mg ranibizumab.

[b] Did not receive any intervention.

[c] Three patients received sham and 0.3 mg ranibizumab, 1 patient received 0.3 mg and 0.5 mg ranibizumab.

[d] Physician's decision, patient's decision, sponsor's decision to terminate study (marked in error), patient noncompliance, patient's condition mandated other therapeutic intervention.

[e] Patients randomized to intervention. All efficacy analyses are intent-to-treat.

[f] he safety-evaluable population included randomized patients who received at least 1 study treatment (ranibizumab or sham injection). Treatment groups for the safety-evaluable population were defined according to the actual treatment received during the 24-month period.

[g] Includes 1 additional patient randomized to sham who received sham and 0.3-mg ranibizumab.

[h] Includes 2 patients randomized to sham who received sham and 0.5-mg ranibizumab and 1 patient who was randomized to 0.3 mg who received 0.3-mg and 0.5-mg ranibizumab.

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6.2 DEMOGRAPHICS AND BASELINE CHARACTERISTICS

Patient demographic and baseline characteristics as well as ocular and anatomic characteristics of the study eye were well balanced overall (in the pooled data as well as within the individual studies): the average age of patients was approximately 62 years (range, 21–91 years), most of the patients were White (approximately 79%), and more than half (57%) of the patients were male. The average duration of diabetes was approximately 16 years (range, 0.1–57.1 years) and patients had mean baseline HbA_{1c} levels of approximately 7.7%. Approximately three-quarters of all patients had previously received some form of treatment for diabetic macular edema; for example, most patients had received macular laser treatment for DME at some point in the past (Table 3).

Table 3 Demographic and Baseline Characteristics: RIDE and RISE Pooled

		Ranibizumab	
Demographic and Baseline Characteristics	Sham (n=257)	0.3 mg (n=250)	0.5 mg (n=252)
Age (y), mean (SD)	62.7 (10.3)	62.2 (10.1)	62.3 (10.1)
Gender: Male, n (%)	140 (54.5%)	146 (58.4%)	145 (57.5%)
Race: White, n (%)	205 (79.8%)	196 (78.4%)	202 (80.2%)
Race: Black or African American, n (%)	34 (13.2%)	32 (12.8%)	27 (10.7%)
Ethnicity: Hispanic or Latino, n (%)	61 (23.7%)	53 (21.2%)	56 (22.2%)
Diabetic history and diabetic control at baseline			
Duration of diabetes (yr), mean (SD)	15.5 (10.3)	15.9 (9.8)	15.8 (9.3)
Mean HbA_{1c}, % (SD)	7.7 (1.4)	7.7 (1.4)	7.6 (1.4)
$HbA_{1c} > 8\%$, n (%)	84 (33.9%)	80 (33.3%)	78 (32.1%)
Best corrected visual acuity			
Number of ETDRS letters, mean (SD)	57.3 (11.2)	56.1 (12.2)	56.9 (11.6)
≤55 letters, n (%)	101 (39.3%)	109 (43.6%)	94 (37.3%)
Other study eye characteristics			
CFT (μm), mean (SD)	457.2 (153.3)	478.6 (162.3)	463.8 (160.4)
Prior treatment for CSME, n (%)	186 (72.4%)	179 (72.0%)	190 (75.4%)
Prior intravitreal anti-VEGF, n (%)	35 (13.6%)	40 (16.0%)	39 (15.5%)
Prior intravitreal steroids, n (%)	64 (24.9%)	68 (27.2%)	81 (32.1%)
Prior focal or grid laser, n (%)	170 (66.1%)	161 (64.4%)	166 (65.9%)

7. EFFICACY IN DIABETIC MACULAR EDEMA

Patients with DME treated with ranibizumab experienced rapid, sustained, and clinically and statistically significant improvements in vision and retinal anatomy compared with patients in the control groups. Results the two studies were consistent with each other, with the benefits of ranibizumab relative to control treatment confirmed in both studies. Treatment benefits observed in the ranibizumab groups at Month 24 were maintained through Month 36, and in general, sham patients crossing over to receive 0.5 mg ranibizumab after Month 24 (referred to as the sham/0.5-mg group) did not experience the same magnitude of benefit as those treated with ranibizumab from the beginning. The efficacy of both doses was similar at both Month 24 and Month 36. The key efficacy results based on the pooled RIDE and RISE data are summarized in Table 4; see also Appendix 4, Tables 4.2–4.8 for additional data.

Table 4 Key Efficacy Data at Month 24 and Month 36: RIDE and RISE Pooled

	24 Month (Primary Analysis)			36 Month		
	Sham (n = 257)	0.3 mg RBZ (n = 250)	0.5 mg RBZ (n = 252)	Sham/ 0.5 mg RBZ (n = 257)	0.3 mg RBZ (n = 250)	0.5 mg RBZ (n = 252)
Primary endpoint: % gaining ≥ 15 letters from baseline	15.2%	39.2%	42.5%	20.6%	44.0%	40.9%
p-value [a]		< 0.0001	< 0.0001		< 0.0001	< 0.0001
Other key efficacy endpoints						
Mean change in BCVA from baseline, letters	2.5	11.7	12.0	4.5	12.4	11.2
p-value		< 0.0001	< 0.0001		< 0.0001	< 0.0001
% Losing < 15 letters from baseline	90.7%	98.0%	96.8%	91.8%	98.0%	96.8%
p-value		0.0002	0.0033		0.0030	0.0137
Mean change in contrast sensitivity from baseline, letters	– 0.2	2.7	2.3	0.5	2.1	1.8
p-value		< 0.0001	< 0.0001		0.0009	0.0033
Mean change in CFT from baseline, μm	– 130	– 255	– 262	– 207	– 262	– 268
p-value		< 0.0001	< 0.0001		0.0061	< 0.0001
Progression of ≥3 steps from baseline [b]	5.0%	1.3%	0.9%	3.8%	1.3%	1.3%
p-value		0.0355	0.0072		0.1219	0.0844
Progression of ≥2 steps from baseline [b]	9.6%	1.7%	2.1%	9.2%	2.6%	3.0%
p-value		0.0004	0.0005		0.0030	0.0044
% patients with macular laser treatment	72.0%	37.6%	27.4%	73.2%	38.8%	29.4%
p-value		< 0.0001	< 0.0001		< 0.0001	< 0.0001
% patients with PRP laser treatment	11.7%	0.8%	1.2%	13.2%	1.6%	2.4%
p-value		< 0.0001	< 0.0001		< 0.0001	< 0.0001

BCVA = best corrected visual acuity; CFT = central foveal thickness; PRP = panretinal photocoagulation. P-values are for testing differences between ranibizumab groups and sham/0.5-mg group with adjustment for baseline visual acuity (≤ 55, > 55 letters), baseline HbA1c (≤ 8%, > 8%), and prior treatment for DME (yes, no).

[a] Results are statistically significant starting from Day 7.

[b] Using the ETDRS diabetic retinopathy severity level.

7.1 VISUAL ACUITY

7.1.1 Primary Endpoint: Proportion of Patients Gaining ≥15 Letters in Best Corrected Visual Acuity

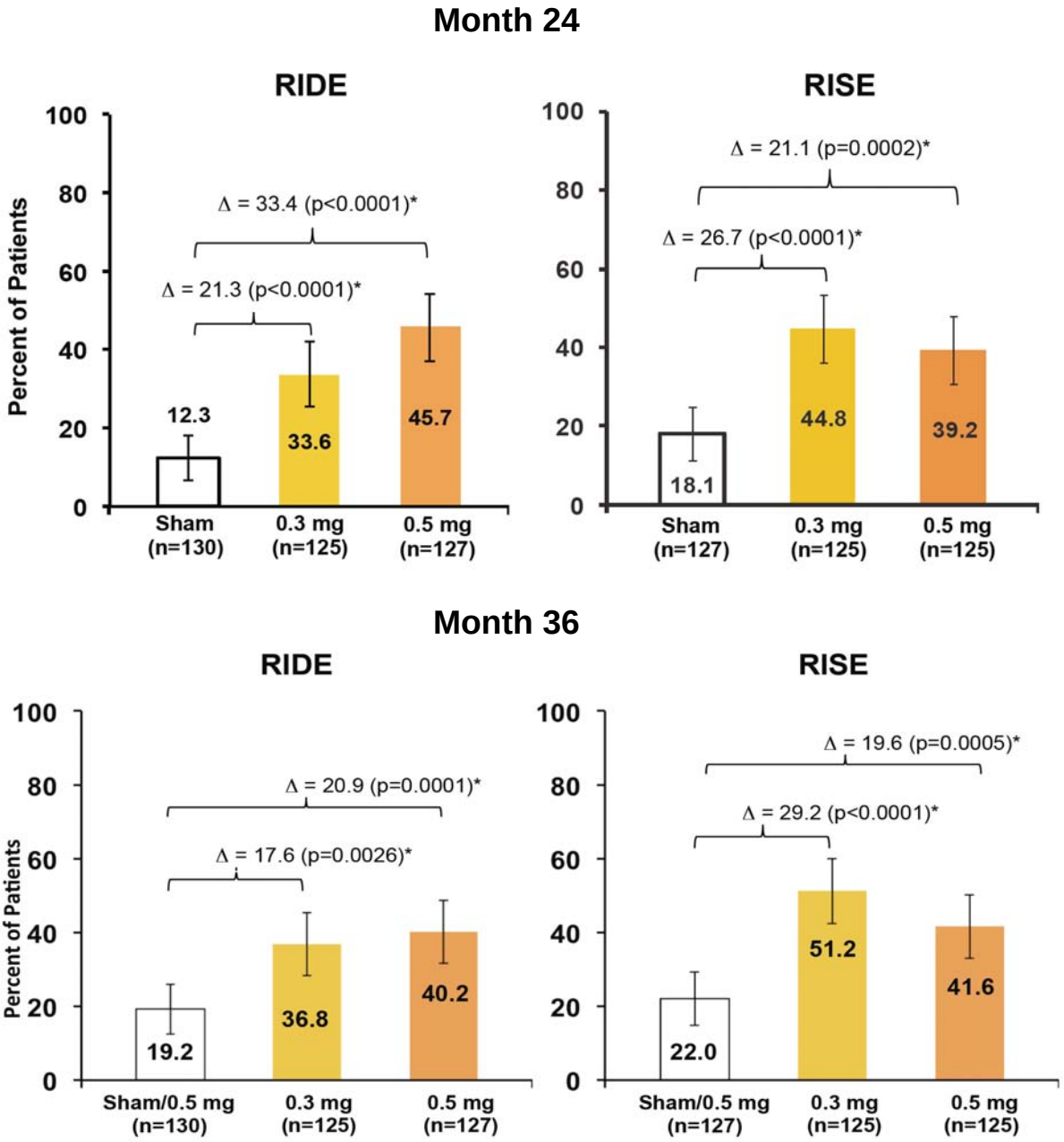
The primary efficacy measure for RIDE and RISE was the proportion of patients who were able to read ≥15 additional letters (approximately three lines) on the standardized eye chart than they could read at the beginning of the study. An improvement of ≥15 letters in best corrected visual acuity (BCVA) is clinically important because it clearly rises above the background level of visual acuity fluctuation over time, is noticeable by and relevant to almost all patients, and has been correlated with significant improvements in functional activities such as reading, cooking, watching television, and driving (Chang et al. 2007; Bressler et al. 2009; Suñer et al. 2009). This efficacy outcome is also accepted by FDA as an approvable endpoint (Csaky et al. 2008).

At Month 24, significantly greater numbers of patients receiving either dose of ranibizumab experienced an improvement of ≥15 letters from baseline compared with sham-treated patients. Pooled results from RIDE and RISE showed that 39.2% of patients receiving 0.3-mg ranibizumab and 42.5% of patients receiving 0.5-mg ranibizumab gained ≥15 letters from baseline in BCVA score at 24 months, compared with 15.2% of patients in the sham group (Table 4). These results were statistically significant ($p < 0.0001$ for each ranibizumab dose group versus the sham group) and the benefit over sham was demonstrated in both RIDE and RISE, starting from 1 month after the first treatment (Figure 10 and Figure 11).

Of note, approximately three-quarters of sham patients received standard-care macular laser treatment through 24 months, and the efficacy outcomes in the RIDE and RISE sham groups at Month 24 were similar to those observed in the macular laser control groups in other recent DME studies (Section 3.2) (DRCR.net 2010; Campochiaro et al. 2011; Mitchell et al. 2011). Thus, the BCVA outcomes for sham patients likely represent the current standard-of-care efficacy benchmark in the treatment of DME.

The treatment benefit observed at Month 24 was sustained through Month 36 for patients in both the 0.3-mg and 0.5-mg ranibizumab groups. For pooled data at Month 36, the percentage of patients who gained ≥15 letters from baseline in BCVA score was 44.0% and 40.9% in the 0.3-mg and 0.5-mg groups, respectively. The percentage of sham patients gaining ≥15 letters from baseline in BCVA (following crossover to active ranibizumab at Month 24 (the sham/0.5-mg group for the Month-36 analysis) increased from 15.2% at Month 24 to 20.6% at Month 36. Despite the sham group crossover, a statistically significant number of patients gained ≥15 letters from baseline at Month 36 with long-term ranibizumab treatment compared with the sham/0.5-mg group patients in whom ranibizumab treatment was delayed for 2 years (Figure 11; see also Appendix 4, Table 4.2 for additional data).

Figure 10 Percentage of Patients Gaining ≥ 15 Letters from Baseline in BCVA Score in the Study Eye at Month 24 and Month 36



Δ=difference in percentage between ranibizumab groups and sham (sham/0.5-mg) group. Vertical bars are 95% confidence interval. Reported percentages and differences versus sham are unadjusted; test and p-value are adjusted for baseline visual acuity (≤55, >55 letters), baseline HbA_{1c} (≤8%, >8%) and prior treatment for DME (yes, no). Missing data were imputed by last observed value.

* Cochran-Mantel-Haenszel chi-squared test (stratified).

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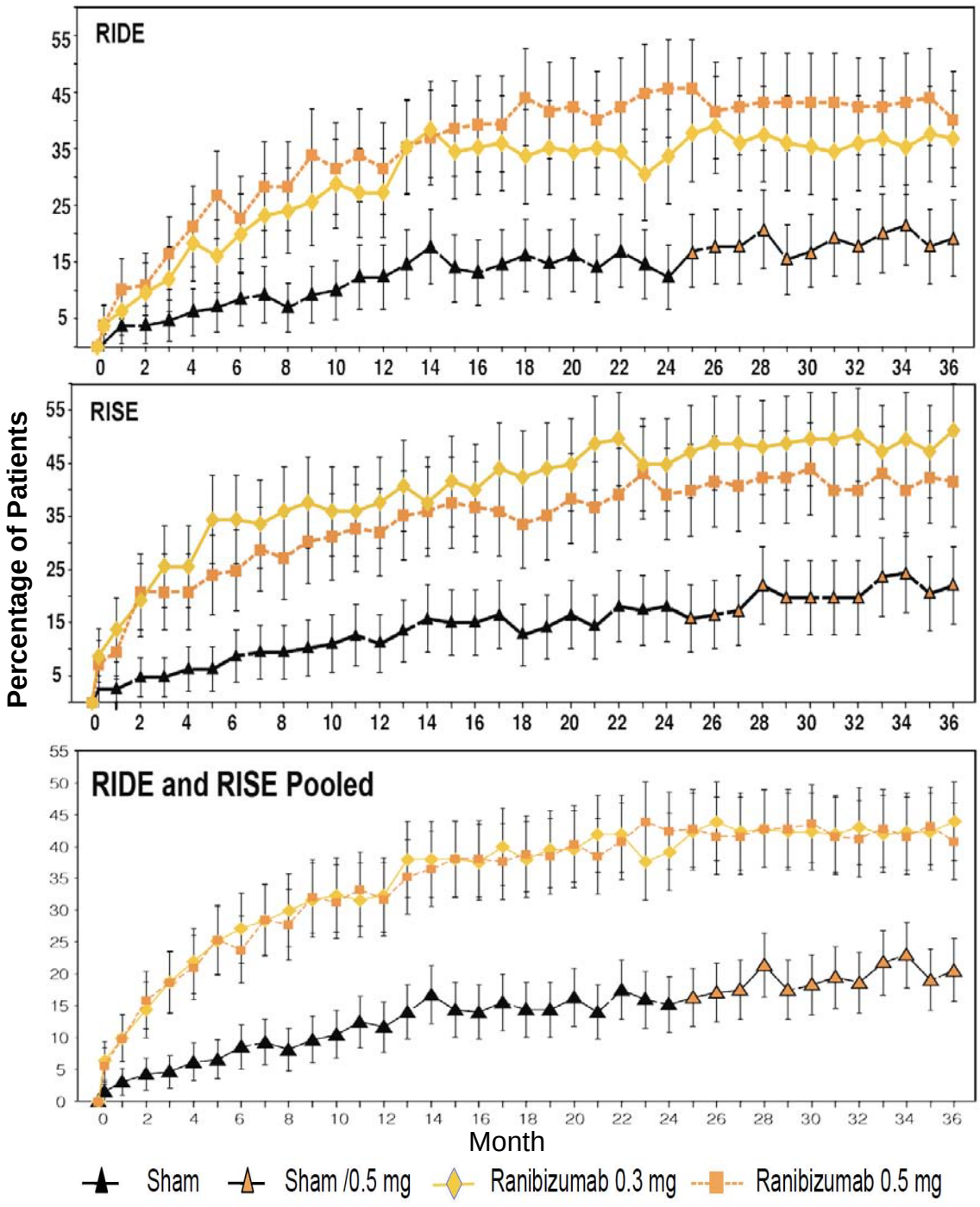
Figure 11 Percentage of Patients Gaining ≥ 15 Letters from Baseline in BCVA Score in the Study Eye over Time



Missing data were imputed by last observed value. Vertical bars are 95% CI of the mean.

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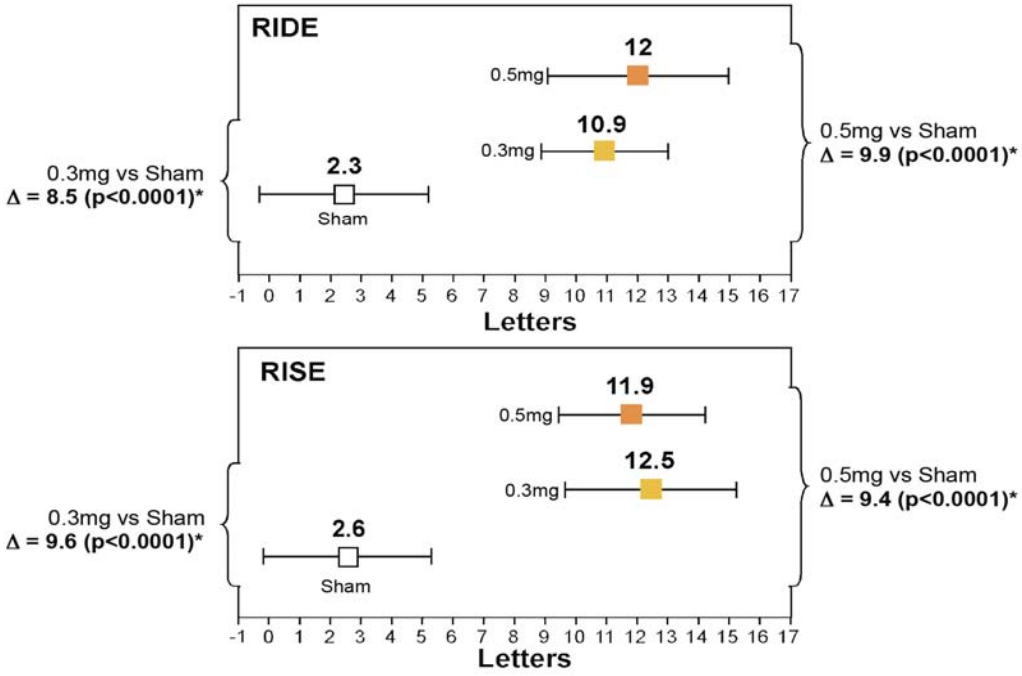
7.1.2 Secondary Endpoint: Mean Change in Visual Acuity over Time

At Month 24, the average BCVA score increased significantly from baseline by 11.7 letters and 12.0 letters in the 0.3-mg and 0.5-mg groups, respectively, compared with 2.5 letters in the sham group ($p < 0.0001$ both pooled and individual study results; Table 4 and Figure 12). The differences between each of the ranibizumab groups and the sham group were statistically significant in favor of ranibizumab starting at Day 7 and at each monthly timepoint thereafter (Figure 13).

The improvement in visual acuity observed at Month 24 was maintained through Month 36 for patients in the 0.3-mg and 0.5-mg groups. Despite the sham group crossover, the ranibizumab groups also experienced substantially larger BCVA increases from baseline compared with the sham/0.5-mg group at Month 36. For pooled data at Month 36, the average BCVA score increased from baseline by 12.4 letters and 11.2 letters in the 0.3-mg and 0.5-mg groups, respectively, and the increase for the sham/0.5-mg group was 4.5 letters (Figure 12); see also Appendix 4, Table 4.3 for additional data.

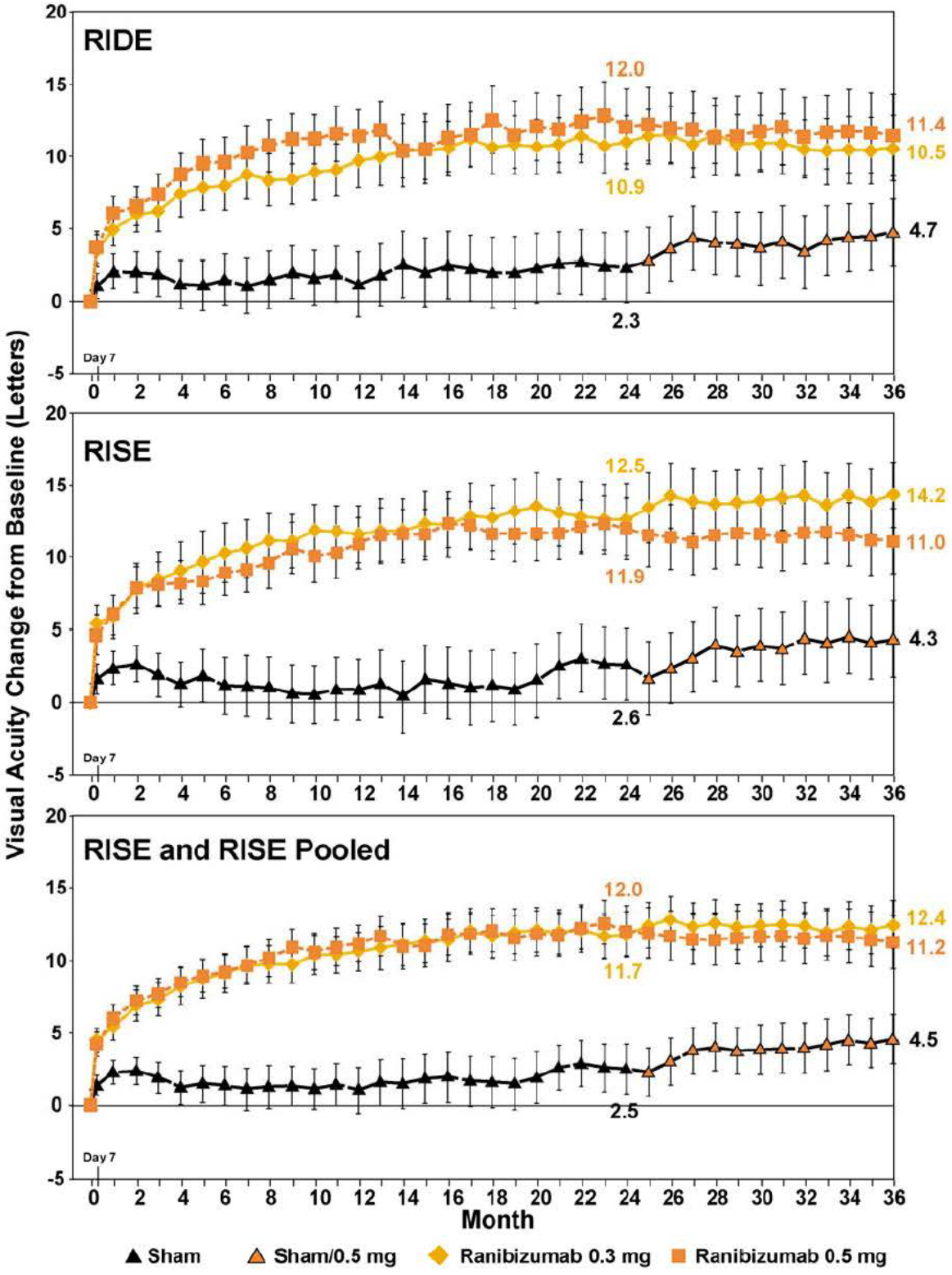
Figure 12 Mean Change in BCVA Score from Baseline in the Study Eye at Month 24



Δ = Adjusted difference in means between ranibizumab groups and sham (sham/0.5-mg) group. Horizontal bars are 95% confidence interval. Reported means are unadjusted; test, Δ, and p-value are adjusted for baseline visual acuity (≤55, >55 letters), baseline HbA_{1c} (≤8%, >8%) and prior treatment for DME (yes, no).

* ANOVA test (stratified).

Figure 13 Mean Change in BCVA Score from Baseline in the Study Eye over Time



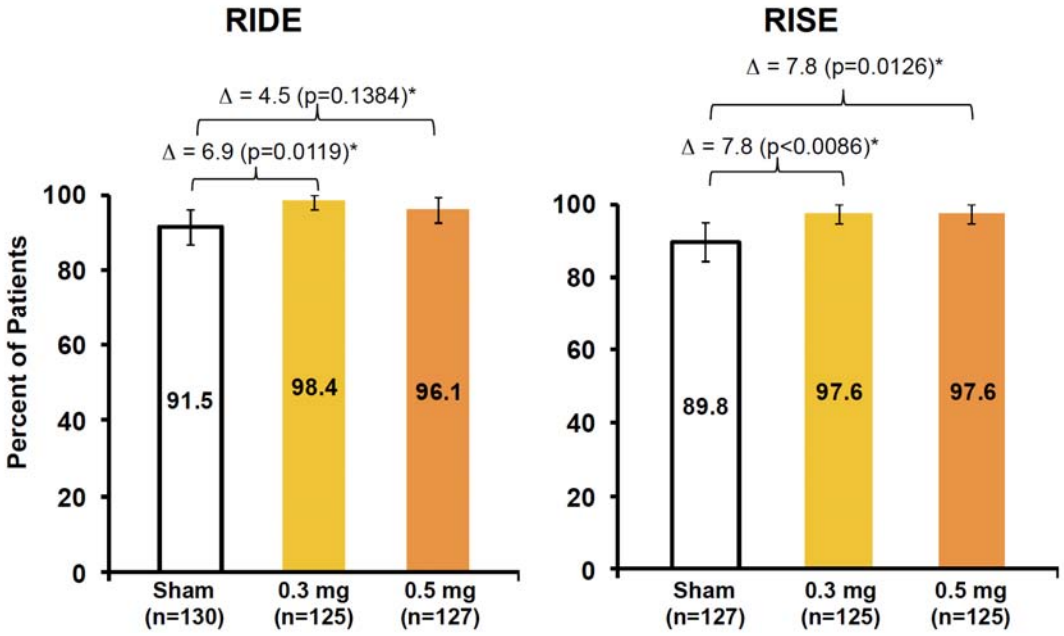
Missing data were imputed by last observed value. Vertical bars are 95% CI of the mean.

7.1.3 Secondary Endpoint: Patients Losing <15 Letters in Best Corrected Visual Acuity

Prevention of significant loss of vision is a key outcome measure; a decrease in vision may prevent a patient with DME from reading, driving, working, or carrying out their activities of daily living unassisted. Thus, a loss of 15 or more letters (or, conversely, prevention of this loss) is a common and important visual acuity endpoint in ophthalmic clinical trials.

At Month 24 in RIDE and RISE, more ranibizumab-treated patients lost fewer than 15 letters from baseline than did sham group patients (Figure 14). Conversely, more sham patients experienced significant (≥15 letter) loss of vision compared with ranibizumab-treated patients. At 24 months, 98% of patients in the 0.3-mg group ($p=0.0002$) and 96.8% of patients in the 0.5-mg group ($p=0.0033$) lost <15 letters in BCVA, compared with 90.7% of patients in the sham group; conversely, nearly 10% of patients in the sham group lost ≥15 letters, compared with 2%–3% of patients in the ranibizumab treatment groups. At Month 36, the proportion of patients who lost <15 letters in BCVA from baseline in the 0.3-mg and 0.5-mg groups remained the same; 91.8% of patients lost <15 letters in the sham/0.5-mg group (Table 4); see also Appendix 4, Table 4.4 for additional data.

Figure 14 Percentage of Patients Losing < 15 Letters from Baseline in BCVA Score in the Study Eye at Month 24



Vertical bars are 95% confidence interval. Reported percentages and differences versus sham are unadjusted, test and p-value are adjusted for baseline visual acuity (≤55, >55 letters), baseline HbA_{1c} (≤8%, >8%) and prior treatment for DME (yes, no). Missing data were imputed by last observed value.

* Cochran-Mantel-Haenszel chi-squared test (stratified).

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7.2 CONTRAST SENSITIVITY

Contrast sensitivity—a measure of the ability to distinguish between finer and finer increments of light versus dark—is another important component of visual function, especially in situations of low light, fog, or glare, when the contrast between objects and their background is reduced. Driving at night, walking down dimly lit stairs, and finding a seat in a dark theater are examples of activities that require good contrast sensitivity for safety. Figure 15 illustrates how visual function can be affected by reduced contrast sensitivity.

Contrast sensitivity was measured by Pelli-Robson Chart for RIDE and RISE. Figure 16 shows the mean change from baseline in contrast sensitivity by Month 24 as measured by the number of letters read correctly on the Pelli–Robson chart. At 24 months, a mean increase from baseline of 2.7 letters was seen in the 0.3-mg group and 2.3 letters in the 0.5-mg group, compared with a mean decrease from baseline of 0.2 letters in the sham group ($p < 0.0001$ for 0.3 mg and 0.5 mg vs. sham; sham-corrected improvement of approximately 0.15–0.20 log contrast sensitivity units). The improvement was maintained at Month 36 (Table 4). Cataract surgery has been reported to result in

contrast sensitivity improvements of 0.25–0.30 log units on the Pelli-Robson chart (Adamsons et al. 1996; Rubin et al. 1993), and these improvements in contrast sensitivity following cataract surgery have been directly linked to improved driving performance (Wood and Carberry 2006).

Figure 15 Impact of Reduced Contrast and Pelli-Robson Chart

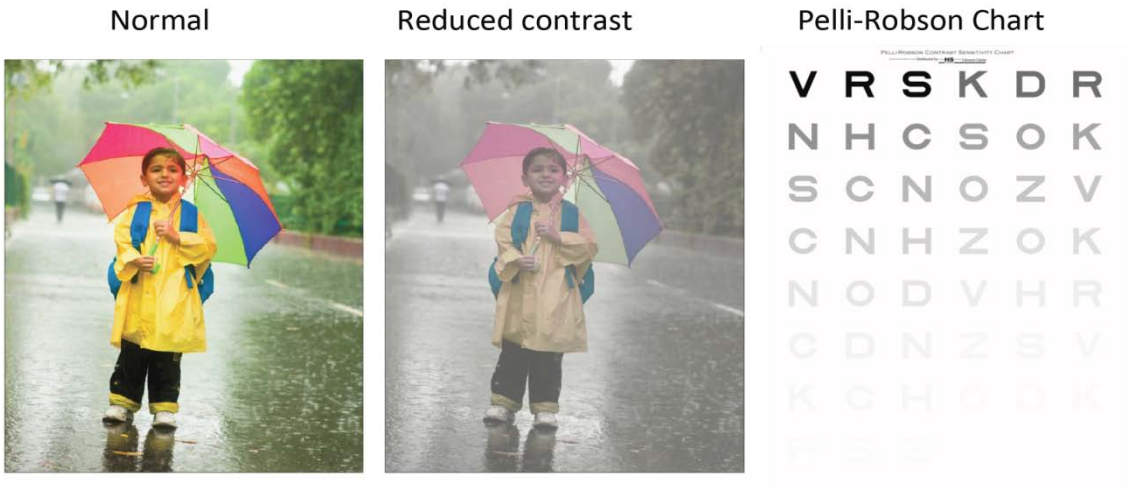
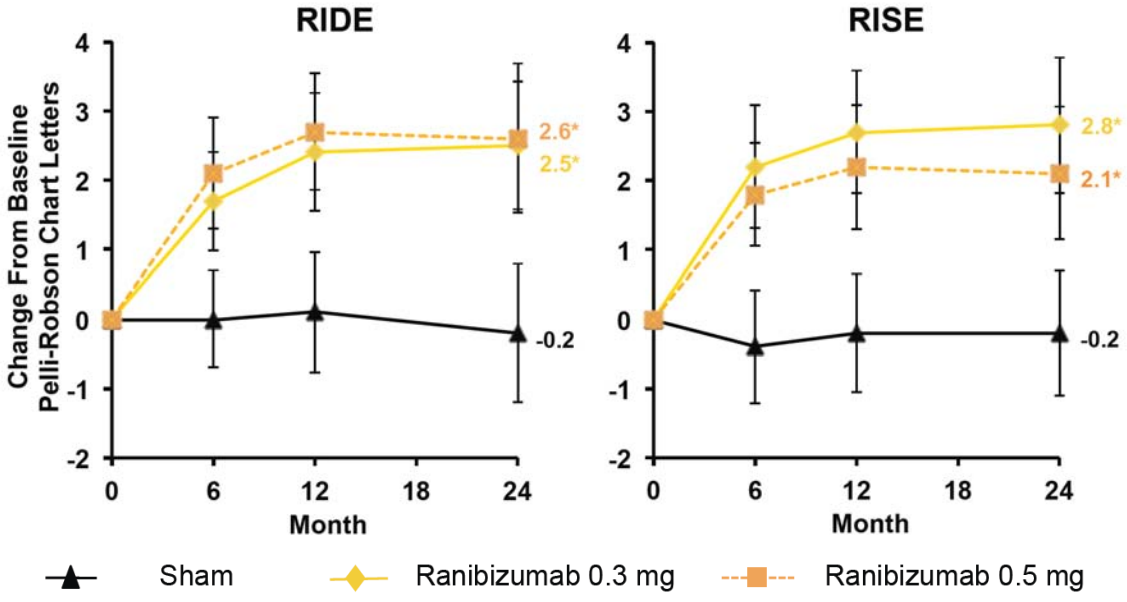


Figure 16 Mean Letter Change from Baseline in Pelli-Robson Chart by Month 24



* p≤0.0001 versus sham. Vertical bars are 95%CI of the mean.

7.3 KEY RETINAL ANATOMIC OUTCOMES

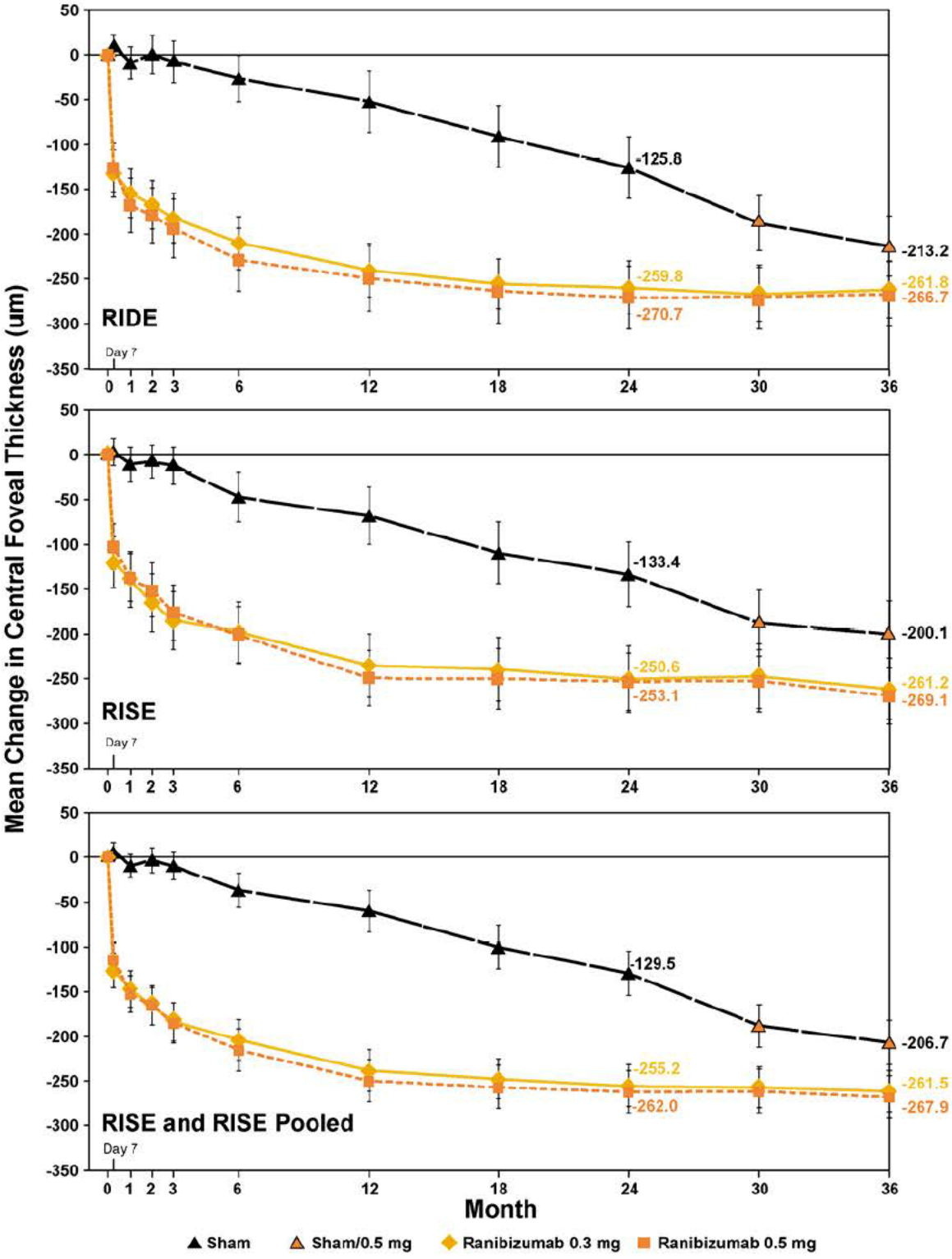
7.3.1 Secondary Endpoint: Mean Change in Central Foveal Thickness over Time

The amount of macular edema in an eye can be evaluated using optical coherence tomography (OCT), a noninvasive imaging tool that allows for a comprehensive cross-sectional evaluation of the macula. Observations available from an OCT scan include the overall retinal thickness, the location and extent of abnormal intraretinal and subretinal fluid collections, the health and/or status of various retinal layers, and the presence or absence of numerous retinal pathologies. In general, patients with clinically significant DME will simultaneously have reduced visual acuity along with increased macular thickness as a result of the presence of edema fluid. A central foveal thickness (CFT) of >250 μm on time-domain OCT is clearly abnormal, and many patients with a CFT greater than this value will have decreased visual acuity. In RIDE and RISE, the CFT on OCT was used both as a diagnostic criterion for study entry, as well as a pharmacodynamic measurement of treatment response.

A rapid and sustained decrease in mean CFT was observed in ranibizumab-treated patients beginning at Day 7 and persisting through Month 24, which is consistent with the visual acuity gains seen at these timepoints. On average, patients treated with 0.3 mg or 0.5 mg ranibizumab showed a substantial decrease in CFT of 126 μm and 114 μm, respectively, 7 days after the first treatment. The average reduction in macular edema continued to improve over time, with a resulting mean decrease of 255 μm and 262 μm for the 0.3-mg and 0.5-mg groups, respectively, at 24 months, while mean change in CFT for patients in the sham group decreased by 130 μm. The difference in the mean change from baseline in CFT between each of the ranibizumab groups and the sham group was statistically significant ($p<0.0001$) at each of the assessment timepoints at which OCT images were graded by the central reading center (Figure 17; see also Appendix 4, Table 4.5 for additional data). At Month 24, a significantly greater number of patients treated with ranibizumab had CFT ≤ 250 μm (Figure 18).

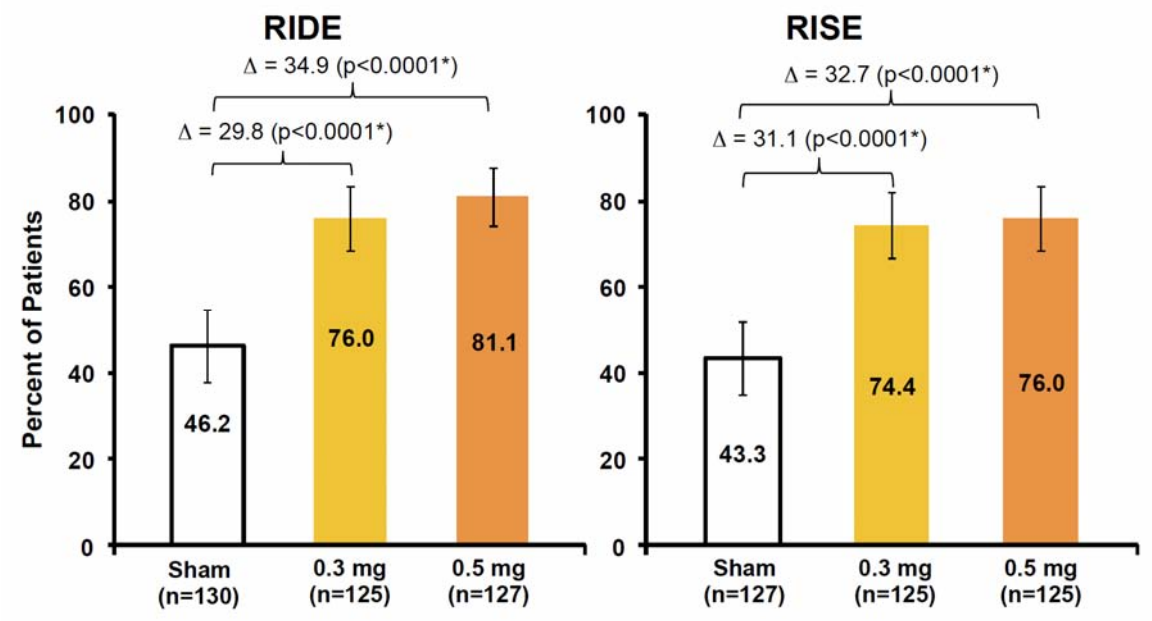
The CFT reduction observed at Month 24 was sustained through Month 36 for patients in 0.3-mg and 0.5-mg groups. For pooled data at Month 36, CFT, on average, decreased from baseline by 262 μm and 268 μm in the 0.3-mg and 0.5-mg groups, respectively; the reduction in CFT from baseline for the sham/0.5-mg group was 207 μm (Table 4); see also Appendix 4, Table 4.5 for additional data.

Figure 17 Mean Change in Central Foveal Thickness from Baseline in the Study Eye at 24 and 36 Months



Vertical bars are 95% confidence interval of the mean.

Figure 18 Percentage of Patients with Central Foveal Thickness ≤250 μm at Month 24



Vertical bars are 95% confidence interval. Reported percentages and differences versus sham are unadjusted, test and p-values are adjusted for baseline visual acuity (≤55, >55 letters), baseline HbA_{1c} (≤8%, >8%) and prior treatment for DME (yes, no).

* Cochran-Mantel-Haenszel chi-squared test (stratified).

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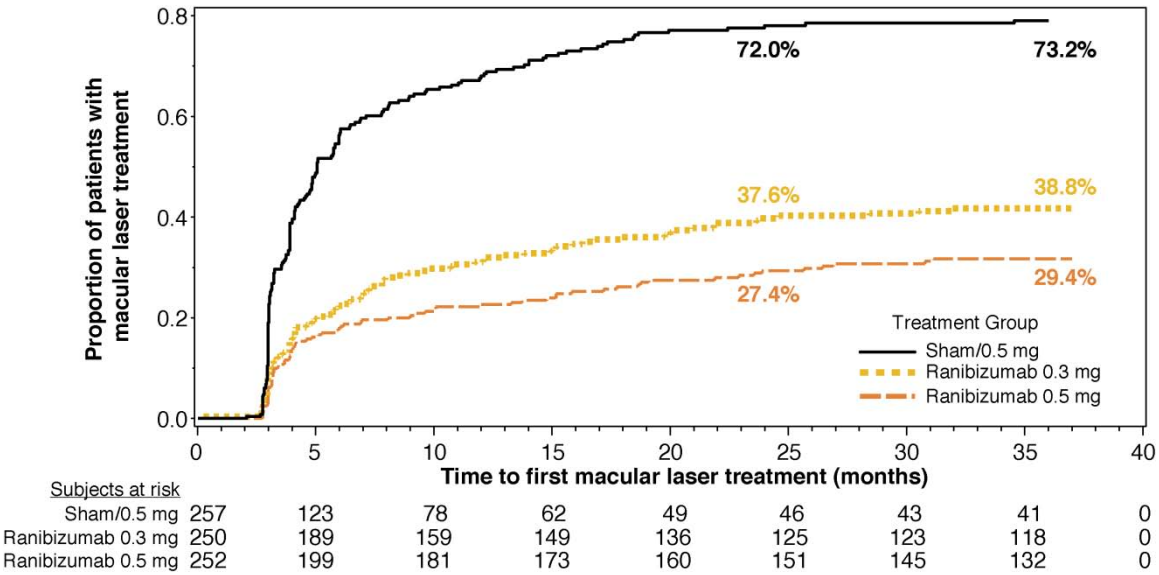
7.4 USE OF MACULAR LASER TREATMENT

Macular laser was administered to patients according to protocol-specified criteria. The need for standard-care macular laser treatment was assessed by the evaluating physician who was masked to patients' treatment assignments.

During the 24-month controlled treatment period, 37.6% and 27.4% of patients in the 0.3-mg and 0.5-mg groups, respectively, received at least one macular laser treatment, compared with 72% of patients in the sham group. As shown in Figure 19, the majority of patients who had macular laser treatment over 24 months in the sham group received their first macular laser treatment within the first 6 months of the study. On average, patients in the 0.3-mg and 0.5-mg groups received less than one macular laser treatment, compared with 1.7 treatments in the sham group ($p < 0.0001$ for each ranibizumab group vs. sham; see Table 4); see also Appendix 4, Table 4.6 for additional data. Although there is no mandatory laser control group in RIDE and RISE, the visual and anatomic outcomes in the sham groups at Month 24 were similar to those observed in laser comparator groups in several recent DME studies (DRCR.net 2010; Campochiaro et al. 2011; Mitchell et al. 2011).

Month 36 results were consistent with those at Month 24. By Month 36, 38.8% of patients in the 0.3-mg group and 29.4% of patients in the 0.5-mg group had received at least one macular laser treatment. Substantially more patients (73.2%) in the sham/0.5-mg group received macular laser treatment by Month 36 compared with the 0.3-mg and 0.5-mg groups; see Appendix 4, Table 4.7 for additional data.

Figure 19 Time to First Macular Laser Treatment by Month 36: RIDE and RISE Pooled



7.5 USE OF PANRETINAL PHOTOCOAGULATION TREATMENT

Panretinal photocoagulation (PRP) is a retinal laser procedure used as treatment for proliferative (end-stage neovascular) diabetic retinopathy (PDR). Along with DME, PDR is another important cause of vision loss in diabetic retinopathy. Development of PDR is often associated with adverse events such as vitreous hemorrhage, traction retinal detachment, and neovascular glaucoma, which are complications that threaten or irreversibly destroy vision and require urgent medical and/or surgical intervention. Although PRP is effective for reducing the risk of catastrophic vision loss in patients who develop PDR, the procedure itself can be associated with significant morbidity, including worsening of contrast sensitivity, loss of color vision, loss of peripheral vision, and reduced quality of central vision (Ip et al. 2012). Patients treated with ranibizumab were less likely to develop proliferative disease, and this was reflected in the lower number of ranibizumab-treated patients undergoing PRP treatment in RIDE and RISE.

At Month 24, 0.8% of patients in the 0.3-mg group and 1.2% of patients in the 0.5-mg group had received at least one PRP treatment, compared with 11.7% of patients in the sham group. By Month 36, 1.6% of patients in the 0.3-mg group and 2.4% of patients in the 0.5-mg group had received at least one PRP treatment compared with 13.2% of

patients in the sham/0.5-mg group (Table 4); see also Appendix 4, Table 4.8 for additional data.

7.6 CHANGE IN RETINOPATHY SEVERITY AND DISEASE STATUS OVER TIME

The anatomic severity of diabetic retinopathy can be evaluated in a standardized way according to the well-validated ETDRS Diabetic Retinopathy Severity Score. The severity score is clinically important because worsening (progression) of disease over time as measured by this scale is linked to significantly increased risk of long-term vision loss and the development of end-stage complications such as PDR. For example, in the Wisconsin Epidemiologic Study of Diabetic Retinopathy, ≥2 and ≥3-step progressions in diabetic retinopathy severity over 4 years were associated with a four- to five-fold increased risk in the development of PDR over the subsequent 6 years (Klein et al. 2001).

The percent of patients with ≥3-step and ≥2-step progression and regression (improvement) from baseline to 24 months in the ETDRS diabetic retinopathy severity level are presented in Figure 20, and Figure 21; see also Appendix 4, Table 4.9 for additional data. At 24 months, fewer patients in the ranibizumab groups had a ≥3-step progression from baseline in the ETDRS diabetic retinopathy severity level (1.3% and 0.9% of patients in the 0.3-mg and 0.5-mg groups, respectively) than in the sham group (5.0% of patients).

In exploratory analyses, many more eyes treated with ranibizumab showed substantial (≥2-step and ≥3-step) improvements in retinopathy severity on fundus photography. The long-term clinical significance of retinopathy improvement on the ETDRS scale remains unclear, but worsening in retinopathy is strongly associated with adverse visual outcomes.

The percentage of patients with a ≥2-step or ≥3-step progression in 0.3-mg and 0.5-mg groups remained relatively stable from Month 24 through Month 36. Patients in the ranibizumab treatment groups had substantially lower rates of diabetic retinopathy progression at Month 36 compared with patients in sham/0.5-mg group (Table 4).

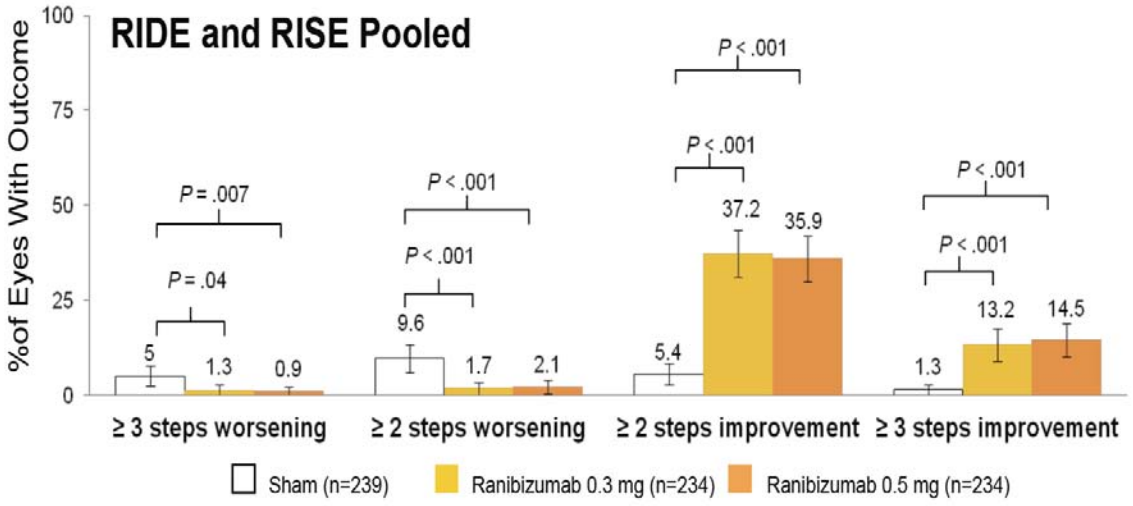
In an exploratory post hoc analysis, worsening of diabetic retinopathy was comprehensively evaluated using a composite outcome that included both changes in diabetic retinopathy severity on fundus photography plus the occurrence of clinically important adverse events or procedures (Figure 22) (Ip et al. 2012). Patients in the ranibizumab groups had a significantly lower risk of diabetic retinopathy progression compared with patients in the sham group ($p<0.001$). Although the goal of RIDE and RISE was primarily to study effects on visual acuity in DME patients, this exploratory finding is of substantial clinical importance, because DME patients are at high risk of

developing proliferative diabetic retinopathy and its associated complications, and a concomitant reduction of these risks is an important additional benefit.

Figure 20 Percentage of Patients with ≥3-Step and ≥2-Step Progression and Regression from Baseline to 24 Months in the ETDRS Diabetic Retinopathy Severity Level

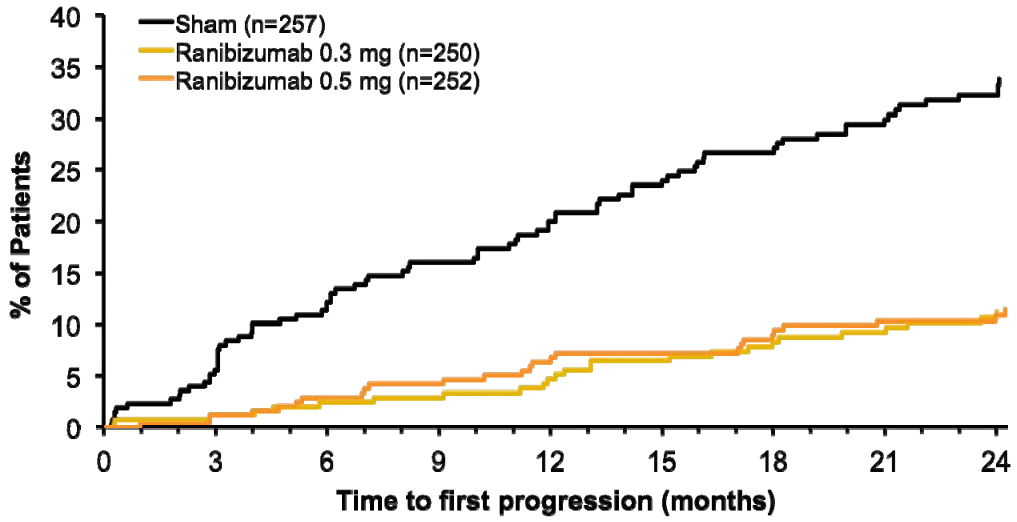
The size of the circles is proportional to the percentage of patients.
* p-value (vs. sham) <0.05.

Figure 21 Changes in in ETDRS Diabetic Retinopathy Severity Level in the Study Eye at Month 24



Vertical bars are 95% confidence intervals (unadjusted).

Figure 22 Time to Development of Proliferative Diabetic Retinopathy in the Study Eye by Month 24: Composite Measurement of Disease Progression



Progression was defined by 1) progression from NPDR (DR severity level <60) at baseline to PDR (DR severity level ≥ 60) at a later timepoint; 2) need for PRP laser; 3) vitreous hemorrhage (AE or slitlamp grade 0 at baseline to >0 at a later timepoint); 4) cases identified by ophthalmoscopy; 5) vitrectomy; 6) iris neovascularization adverse event; or 7) retinal neovascularization adverse event.

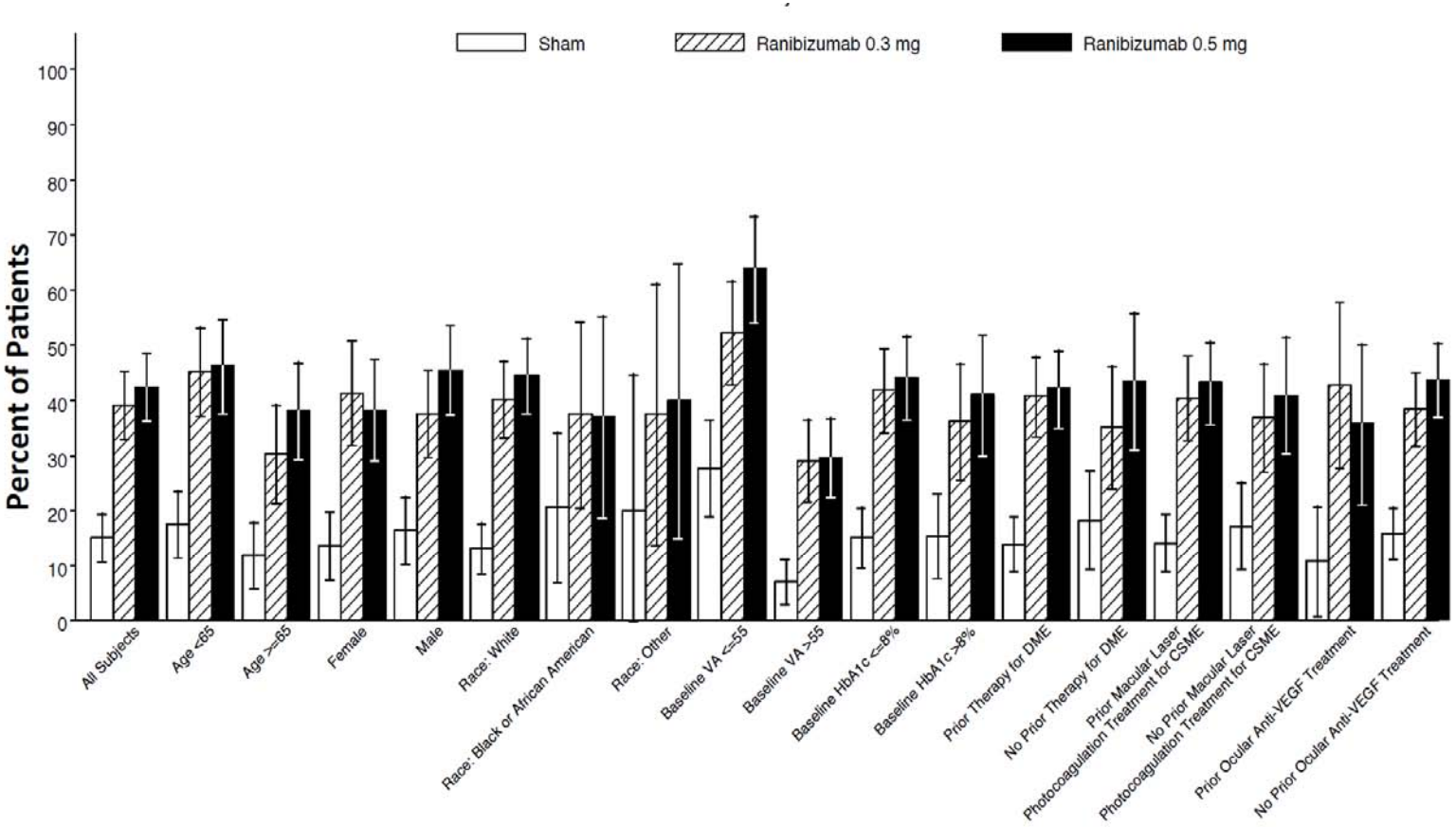
DR = diabetic retinopathy; PRP = proliferative diabetic retinopathy.

Log rank test $p < 0.001$ vs. sham.

7.7 SUBGROUP ANALYSES

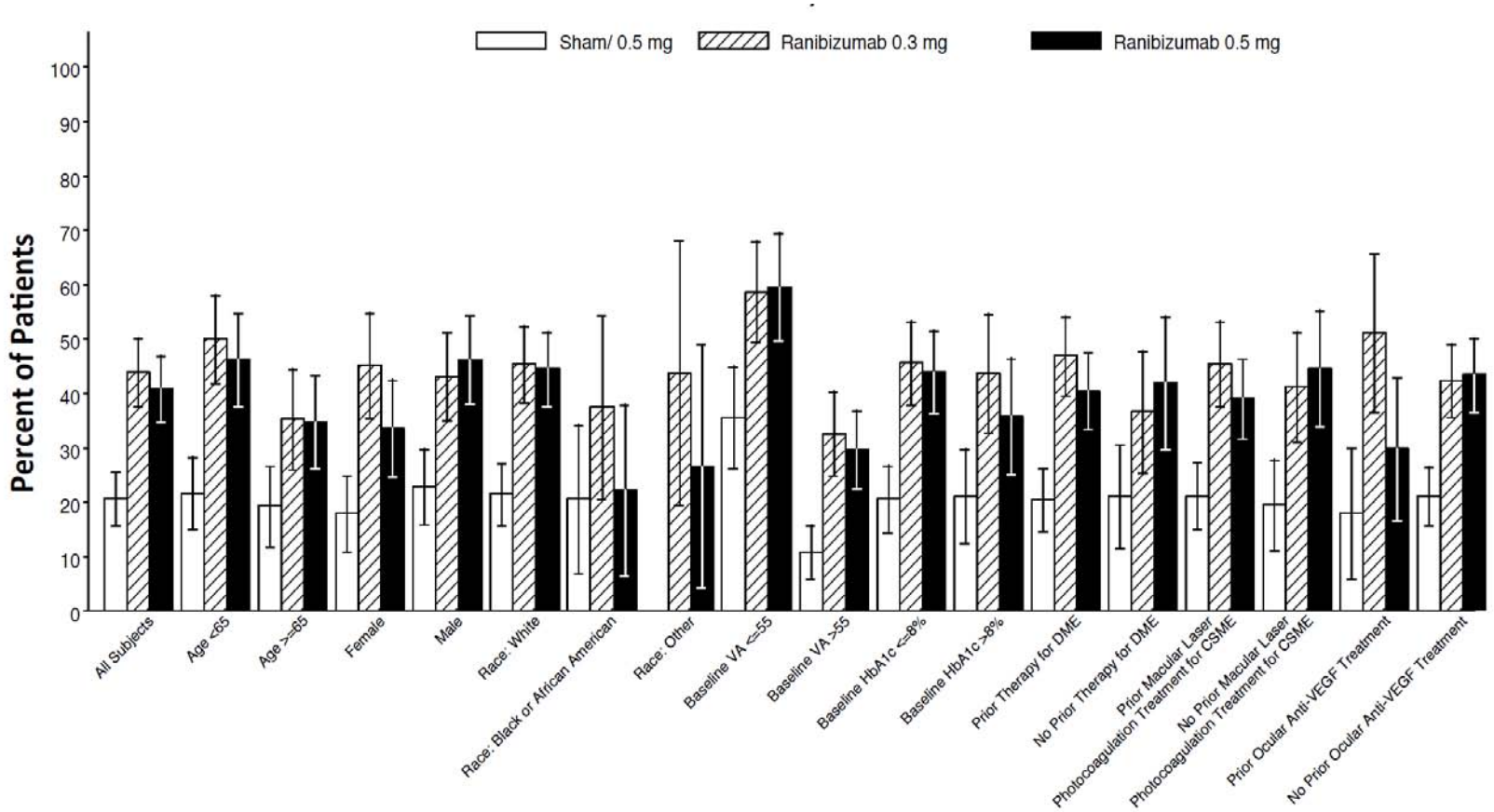
Visual acuity outcomes at Month 24 and Month 36 were examined in all patient subgroups defined by key baseline factors, including those defined by baseline HbA_{1c} ($\leq 8\%$ or $>8\%$), baseline visual acuity (≤ 55 or >55), anatomic type of macular edema (with predominantly focal edema), prior treatment for macular edema, prior macular laser treatment, prior ocular anti-VEGF treatment, sex, age, or race. In all subgroups examined, a benefit was seen with both doses of ranibizumab compared with sham control (Figure 23 and Figure 24).

Figure 23 Percentage of Patients Gaining ≥15 Letters in BCVA Compared with Baseline at Month 24 by Subgroup: RIDE and RISE Pooled



CSME = clinically significant macular edema; HbA_{1c} = glycosylated hemoglobin; VA = visual acuity; VEGF = vascular endothelial growth factor.
Note: Baseline was the last observation prior to initiation of study treatment. Vertical bars are 95%CI of the percentage.

Figure 24 Percentage of Patients Gaining ≥15 Letters in BCVA Score Compared with Baseline at Month 36 by Subgroup: RIDE and RISE Pooled



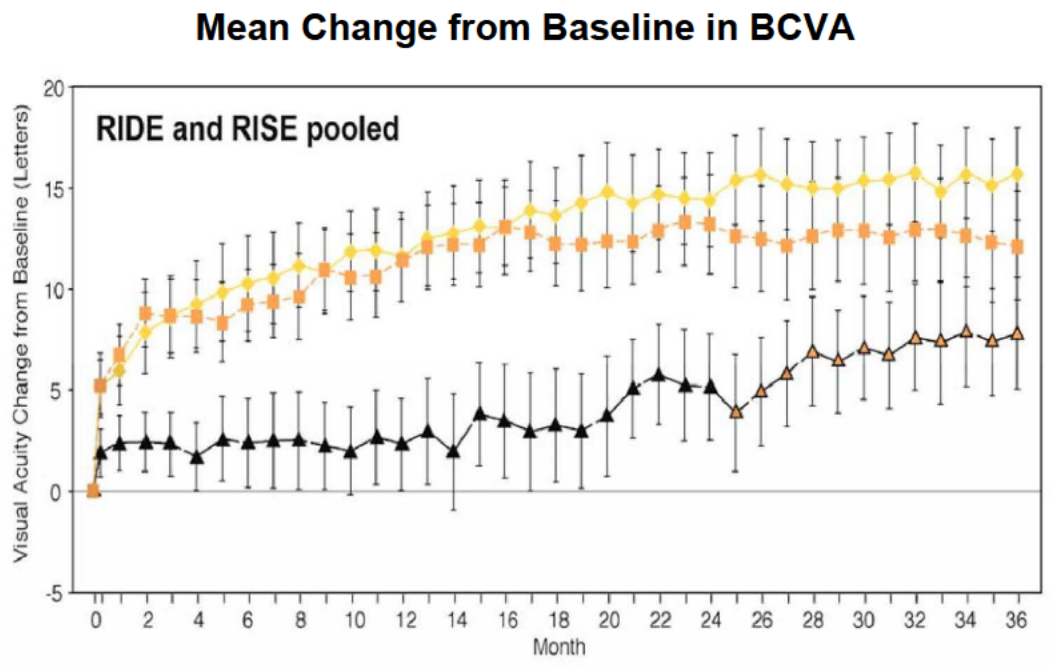
CSME = clinically significant macular edema; HbA_{1c} = glycosylated hemoglobin; VA = visual acuity; VEGF = vascular endothelial growth factor.
Note: Baseline was the last observation prior to initiation of study treatment. Vertical bars 95%CI of the percentage.

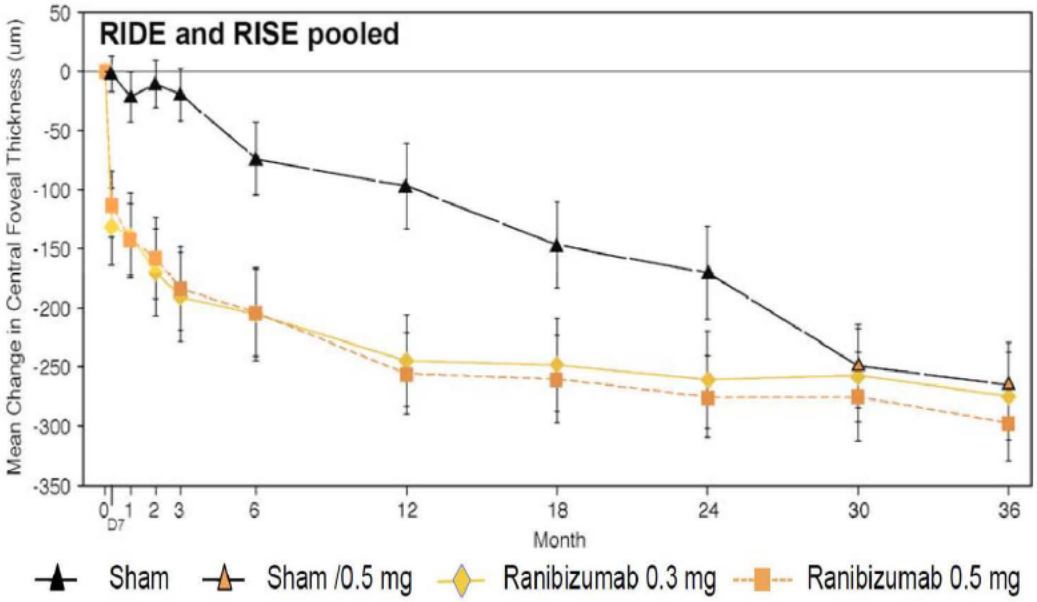
7.8 ANALYSIS OF OUTCOMES IN SHAM PATIENTS CROSSING OVER TO RANIBIZUMAB IN YEAR 3

To better understand the effects of crossover from sham to monthly 0.5-mg ranibizumab, the mean change from baseline in BCVA score and CFT over time up to Month 36 was plotted for the subgroup of patients still receiving study drug after Month 24 (Figure 25). For this subgroup, all but 2 patients had crossed over to the 0.5-mg group. For sham/0.5-mg patients who received treatment during Month 25 through Month 36, gains in BCVA and decreases in CFT were seen after Month 25. By Month 36, on average, BCVA increased by 2.8 letters and CFT decreased by 98.4 μm for sham patients who received ranibizumab treatment.

Because crossover patients received 12 months of 0.5 mg ranibizumab treatment, some comparison can be made between this group and patients who were originally randomized to ranibizumab at 1 year. The changes in visual acuity and CFT at 12 months after the first dose of ranibizumab, summarized in Table 5, show similar reductions in CFT in all groups following sham crossover. However, the improvements in BCVA seen in the sham/0.5-mg group at 12 months after the first dose of ranibizumab did not match the magnitude of those seen during the first year for groups originally randomized to ranibizumab. While these data should be interpreted cautiously because the groups were no longer comparable prior to first ranibizumab treatment, they suggest that a 2-year delay in treatment with ranibizumab may result in some level of irretrievable vision loss.

Figure 25 Mean Change from Baseline in BCVA and Central Foveal Thickness in the Study Eye by Visit during the 36-Month Treatment Period: Randomized Patients Who Received at Least One Study Drug Injection after Month 24





Vertical bars are 95% CI of the mean.

Table 5 Changes in the Study Eye at 12 Months after the First Dose of Ranibizumab for Key Efficacy Outcomes: RIDE and RISE Pooled

	Sham Crossover 0.5 mg RBZ (n=191)	Ranibizumab 0.3 mg (n=250)	Ranibizumab 0.5 mg (n=252)
Total number of RBZ injections by first 12 month RBZ treatment [a], mean (SD)	10.0 (2.0)	10.6 (2.6)	10.9 (2.2)
BCVA (letters)			
Pre RBZ treatment [b], mean (SD)	62.0 (15.3)	56.1 (12.2)	56.9 (11.6)
12-mo post RBZ treatment, mean (SD)	64.8 (14.8)	67.8 (15.0)	68.9 (14.1)
Change from pre-treatment, mean (SD)	2.8 (9.8)	10.6 (10.6)	11.1 (10.1)
Gain of ≥15 letters from pre-treatment, n (%)	14 (7.3%)	81 (32.4%)	80 (31.7%)
Central foveal thickness (μm):			
Pre RBZ treatment [b], mean (SD)	292.5 (167.2)	478.6 (162.3)	463.8 (160.4)
12-mo post RBZ treatment, mean (SD)	194.1 (118.2)	223.4 (136.2)	201.9 (107.3)
Change from pre-treatment, mean (SD)	–98.4 (142.8)	–237.9 (186.1)	–249.3 (194.8)

BCVA=best corrected visual acuity; RBZ=ranibizumab.

[a] Actual treatment duration for sham crossover group is 11 months.

[b] Prior to any RBZ treatment: Month 24 for sham/0.5-mg group; Month 0 for the other two groups.

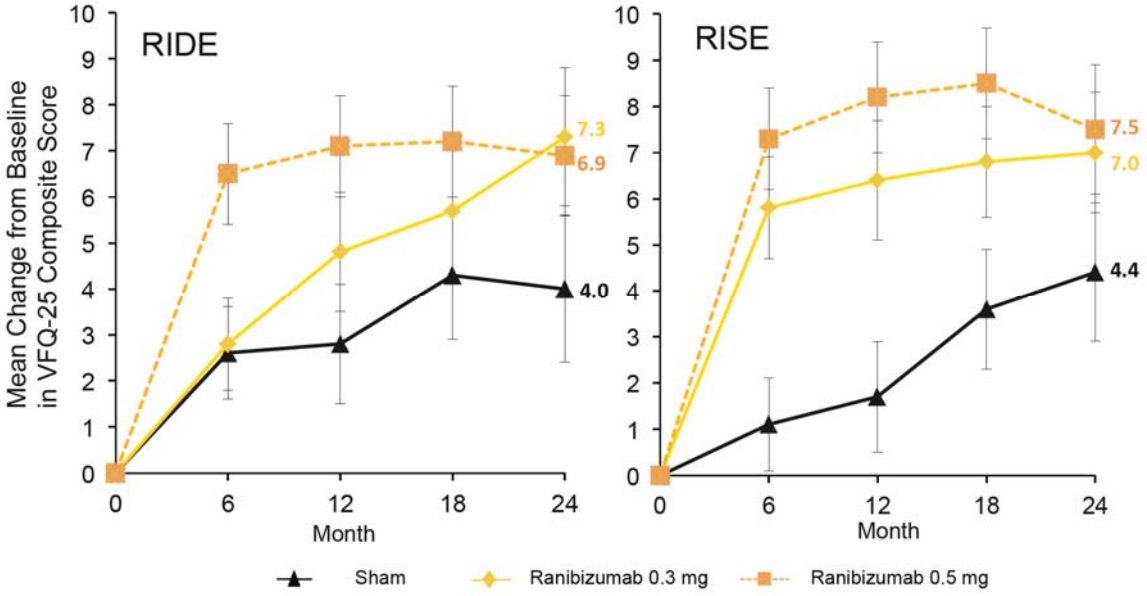
7.9 PATIENT REPORTED OUTCOMES

The National Eye Institute Visual Functioning Questionnaire (NEI VFQ-25) is a patient-reported questionnaire administered in RIDE and RISE to measure a patient's perceived ability to perform activities of daily life that require vision. The NEI VFQ-25 captures the way both eyes function together in everyday life, which includes 1 general health item in addition to 11 subscales that assess general vision, ocular pain, near vision, distance vision, social function, mental health, role limitations, dependency, driving, color vision, and peripheral vision. A higher score on the NEI VFQ–25 indicates better visual function and better vision-related quality of life. The reliability and validity of the NEI VFQ–25 has been demonstrated in a variety of eye conditions including diabetic retinopathy (Mangione et al. 2001). In addition, the NEI VFQ-25 has been shown to correlate with visual acuity (independent of the degree of retinopathy) and be responsive to change among DME patients (Klein et al. 2001; Turpcu et al. 2012).

By Month 24, compared with the sham group, the ranibizumab groups demonstrated consistent trends in better NEI VFQ-25 results over time, even though only one eye per patient was treated. The mean change from baseline in NEI VFQ-25 composite scores for RIDE and RISE by Month 24 are shown in Figure 26. Improvements over time observed in the sham groups may be the result of either placebo effects or macular laser

treatments. Changes in NEI VFQ-25 subscales from baseline to Month 24 are summarized in Appendix 5, Table 5.1.

Figure 26 Mean Change from Baseline in NEI VFQ-25 Composite Score



Error bars limits are ±1 standard error of the mean.

8. OVERVIEW OF CLINICAL PHARMACOLOGY

8.1 PHARMACOKINETICS

Ranibizumab is administered as an intravitreal injection, with the site of action in the retina. Following administration into the eye, ranibizumab is absorbed from the eye into the systemic circulation, where it is measureable in serum. This section will discuss the clinical pharmacokinetics of ranibizumab exclusively because the clinical pharmacology with relation to dose is discussed in the Efficacy and Safety sections.

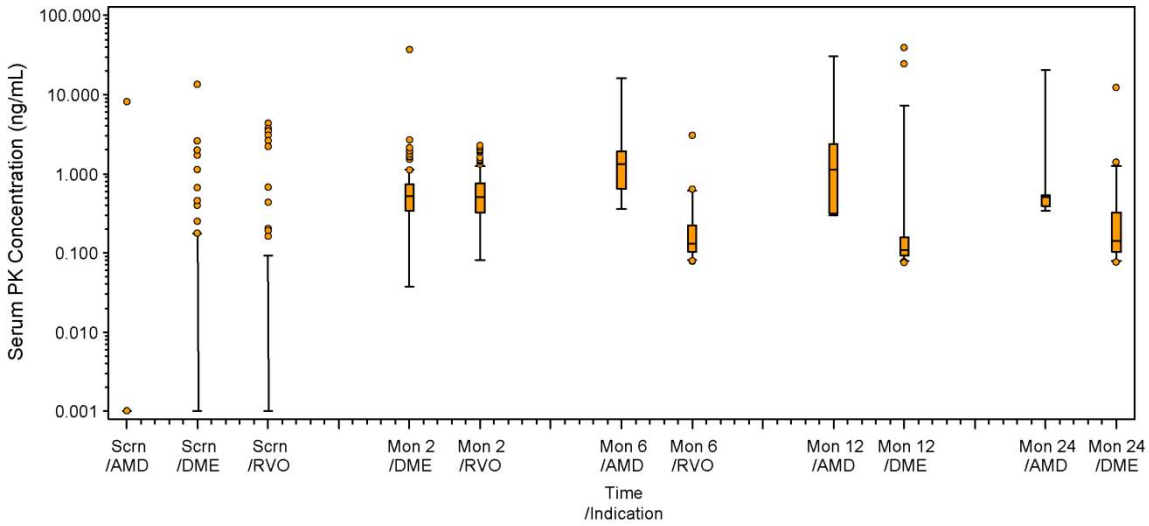
Systemic ranibizumab pharmacokinetics previously has been well described in patients with age-related macular degeneration (AMD) and retinal vein occlusion (RVO) by use of a population pharmacokinetics (PK) approach. Ranibizumab was absorbed from vitreous to systemic circulation with a half-life of 9 days, and it was quickly eliminated from circulation with a half-life of 3 hours. Thus, the apparent absorption rate-limited systemic half-life was 9 days.

The clinical pharmacology of ranibizumab in DME was assessed in RIDE and RISE to determine if the pharmacokinetics of ranibizumab in DME patients were similar to those in other approved indications. By comparing observed systemic concentrations of ranibizumab and identifying baseline patient characteristics that might affect these concentrations, the potential need for dose adjustment was evaluated. Specifically, covariates such as age, serum creatinine clearance, baseline visual acuity, baseline foveal thickness, and baseline leakage area were evaluated.

Serum samples were collected at various timepoints following ranibizumab administration, including Days 3, 7, 14, and 30 postdose. Observed ranibizumab concentrations were similar at postdose timepoints common to the DME, RVO, and AMD studies for those patients who had detectable concentrations. Figure 27 matches timepoints from the different studies and shows that the serum concentrations were similar.

The PK assay for ranibizumab in serum was changed to a more sensitive platform after the pivotal AMD study and before the RVO and DME pivotal studies. The AMD assay had a limit of quantification (LOQ) of 0.3 ng/mL and the RVO and DME assay platform had an LOQ of 0.075 ng/mL. The more sensitive platform for the analysis of RVO and DME samples resulted in more patients showing measurable levels of serum ranibizumab at pre-dose timepoints and thus, in some cases, the detection of lower concentrations pulled down the mean serum concentrations for the RVO and DME studies as shown in Figure 27 at Months 12 and 24.

Figure 27 Serum Pharmacokinetic Concentrations over Time by Indication



Scrn=screening. PK draws are done pre-injection at visits where injections are administered. Zero (0) concentrations are replaced with 0.001 to accommodate the log scale. The analysis did not include any PK serum concentrations collected in DME patients after ranibizumab treatment in the fellow (non-study) eye. For any treatment and sampling timepoint, if one-third or fewer values were less than reportable, they were set to one-half of the limit of quantification (LOQ). For AMD, the LOQ was 0.3 ng/mL, while for RVO and DME the LOQ was 0.075 ng/mL. Whiskers extend from the 5th to the 95th percentile.

Of note, for trough (minimum concentration) samples at Months 12 and 24 in the DME studies, 74%–81% and 58%–66% of tested serum samples showed concentrations that were less than reportable (LTR) for the 0.3-mg and 0.5-mg ranibizumab dose groups, respectively. These results are consistent with rapid systemic elimination of ranibizumab and suggest no meaningful accumulation of ranibizumab throughout the treatment period. In addition, the lower percentage of LTR results in the 0.5-mg group suggests higher systemic concentration compared with the 0.3-mg group.

Following analysis of the AMD and RVO datasets, five covariates (including age, serum creatinine clearance, baseline visual acuity, baseline foveal thickness, and baseline leakage area) were examined for potential effect on systemic exposure of ranibizumab in DME patients. Of these, creatinine clearance (CrCL) had a statistically significant but moderate effect on ranibizumab systemic exposure. However, considering that serum is not the site of action for ranibizumab and that the observed systemic concentrations were consistently low, the change in concentration due to CrCL was deemed not to be clinically significant, and thus did not suggest the need for a dose adjustment. This conclusion is consistent with population pharmacokinetics analysis results for AMD and RVO.

9. SAFETY

9.1 SUMMARY

The safety of ranibizumab has been evaluated in more than 10,000 patients in investigational clinical trials sponsored by Genentech or Novartis. Novartis Pharma AG is Genentech's development and marketing partner for ranibizumab outside the U.S. Patient exposure in clinical practice is estimated to exceed 1.2 million patient treatment-years since initial approval in 2006 in any indication.

Key known and potential risks of ranibizumab based on the AMD and RVO indications are reflected in the currently approved U.S. Product Label (Appendix 1). Intravitreal injections, including those with ranibizumab, have been associated with endophthalmitis, and retinal detachments. Increases in intraocular pressure are observed following intravitreal injections; these are typically transient and managed expectantly or with topical medications. With regard to systemic safety, there is a potential risk of arteriothromboembolic events (ATEs) following intravitreal use of VEGF inhibitors, including stroke, myocardial infarction, and vascular death. A low rate of ATEs has been observed in the ranibizumab clinical trials in AMD and RVO and is described in the WARNINGS AND PRECAUTIONS section of the currently approved U.S. Product Label.

The safety analysis of ranibizumab in the DME population sought to determine if any unexpected or more frequent safety events emerged compared with the other indicated populations, and if the overall benefit–risk profile warranted a similar or different dose of ranibizumab in DME than in other approved indications.

Pooled safety data from RIDE and RISE are presented based on the safety-evaluable population, unless otherwise noted. Patients who received any ranibizumab study treatment at any time during the study period are classified as ranibizumab patients for purposes of this safety analysis. Primary safety analyses were performed after all patients had completed 24 months of follow-up; the 24-month data represent the sham-controlled period of the study. Sham-injection group patients were allowed to cross over and receive 0.5 mg ranibizumab after Month 24, and therefore, Months 25–36 were no longer sham-controlled. Accordingly, direct comparison between the ranibizumab and sham crossover groups is not possible after Month 24, because of the 12 months of ranibizumab exposure received in the crossover group. Safety data collected through Month 36 were evaluated to assess whether the longer-term safety profile of ranibizumab was consistent between Month 24 and 36 and to assess safety between the studied doses.

The analyses for ocular and non-ocular safety in RIDE and RISE are summarized separately. The interpretation of adverse events (AEs) and serious adverse events (SAEs) with respect to potential ranibizumab causality was based, along with other factors, on dose-dependent trends in event rate imbalances, biologic plausibility in association with known effects of VEGF inhibition, and previous safety observations in

ranibizumab clinical trials for other indications. For many of the AEs of interest, the assessment of causality is limited by the small number of these events in the RIDE and RISE studies. Therefore, the only conclusion that can be drawn is that a causal relationship between ranibizumab therapy and the event cannot be excluded.

Overall, ranibizumab was generally well tolerated in DME patients through 36 months, with a safety profile generally similar to that established in patients with neovascular AMD. Key adverse events are summarized below:

- Ocular safety
  - The most common ocular AEs reported more frequently in the ranibizumab groups relative to the sham group were those primarily related to injection procedures (e.g., conjunctival hemorrhage, increased IOP, eye pain).
  - The per-injection rate of procedure-related AEs was low and consistent with other large Phase III studies of ranibizumab in other diseases.
  - Key ocular SAEs of endophthalmitis, traumatic cataract, retinal tear, retinal detachment, increased IOP, and intraocular inflammation were uncommon in ranibizumab-treated patients.
- Non-ocular safety
  - Overall rates of non-ocular SAEs were higher in the 0.5-mg group than the 0.3-mg group at 24 and 36 months.
  - Numerical imbalances compared with the sham group with a trend toward dose dependency (0.5-mg group higher than 0.3-mg group) were observed for the non-ocular SAEs of all-cause mortality, stroke, and hypertension.
  - The rates of myocardial infarction (MI) were comparable among treatment groups at 24 months. At Month 36, a numerically higher rate of MI was observed for the 0.3-mg group compared with the 0.5-mg group.
  - A numerical imbalance compared with the sham group with a trend toward dose dependency was observed for wound healing AEs. One event in 1 patient in the 0.5-mg group was reported as serious.

Table 6 presents a summary of ocular and non-ocular AE and SAE rates at 24 and 36 months observed in the ranibizumab and sham groups in the pooled RIDE and RISE studies.

9.2 OVERALL EXPOSURE

Of the 759 patients enrolled in RIDE and RISE, 750 received study treatment and were classified as safety-evaluable patients: 500 safety-evaluable patients were treated with ranibizumab, along with 250 safety-evaluable patients in the sham group during the 24-month controlled–treatment period. During this time, ranibizumab-treated patients received an average of 21.2 injections of a possible total of 25 injections (Table 7).

During the 36-month treatment period in both DME studies, patients in either the 0.3-mg or 0.5-mg ranibizumab groups received a mean of 29 out of 35 total possible injections. Patients in the sham group who crossed over to 0.5 mg ranibizumab (n = 190) received a mean of 10 out of 11 possible injections (Table 7) in the study eye during 12 months of ranibizumab treatment (third year of study treatment).

Table 6 Summary of Key Safety Events for RIDE and RISE

Event Type	24-Month Sham-Controlled Period			36-Month Study Period	
	Sham (n=250)	0.3 mg Ranibizumab (n=250)	0.5 mg Ranibizumab (n=250)	0.3 mg Ranibizumab (n=250)	0.5 mg Ranibizumab (n=249)
Ocular events, study eye					
Any adverse event	216 (86.4%)	216 (86.4%)	212 (84.8%)	221 (88.4%)	217 (87.1%)
Adverse events leading to treatment discontinuation	12 (4.8%)	1 (0.4%)	3 (1.2%)	2 (0.8%)	4 (1.6%)
Any serious adverse event	16 (6.4%)	8 (3.2%)	19 (7.6%)	12 (4.8%)	26 (10.4%)
Key serious adverse events					
Endophthalmitis	0	2 (0.8%)	2 (0.8%)	4 (1.6%)	2 (0.8%)
Retinal detachment	1 (0.4%)	0	1 (0.4%)	0	1 (0.4%)
Vitreous hemorrhage	7 (2.8%)	0	2 (0.8%)	1 (0.4%)	3 (1.2%)
Non-ocular event					
Any adverse event	214 (85.6%)	222 (88.8%)	209 (83.6%)	227 (90.8%)	220 (88.4%)
AEs leading to treatment discontinuation	9 (3.6%)	15 (6.0%)	15 (6.0%)	20 (8.0%)	19 (7.6%)
Any serious adverse event	83 (33.2%)	81 (32.4%)	91 (36.4%)	10 (40.0%)	116 (46.6%)
Key serious adverse events					
Hypertension serious adverse events [a]	1 (0.4%)	3 (1.2%)	6 (2.4%)	4 (1.6%)	10 (4.0%)

[a] Hypertension serious adverse events include hypertension, hypertensive crisis, and hypertensive emergency.

[b] Wound healing complication adverse events include open wound, postoperative wound infection, wound infection and wound complication.

[c] One wound healing adverse event in the 0.5 mg group was reported as a serious adverse event.

Table 6 Summary of Key Safety Events for RIDE and RISE (cont.)

Event Type	24-Month Sham-Controlled Period			36-Month Study Period	
	Sham (n=250)	0.3 mg Ranibizumab (n=250)	0.5 mg Ranibizumab (n=250)	0.3 mg Ranibizumab (n=250)	0.5 mg Ranibizumab (n=249)
Key events					
Death	3 (1.2%)	7 (2.8%)	11 (4.4%)	11 (4.4%)	16 (6.4%)
Vascular death	3 (1.2%)	5 (2.0%)	6 (2.4%)	8 (3.2%)	8 (3.2%)
Arterial thromboembolic adverse events	27 (10.8%)	21 (8.4%)	22 (8.8%)	32 (12.8%)	31 (12.4%)
Stroke	4 (1.6%)	3 (1.2%)	8 (3.2%)	5 (2.0%)	12 (4.8%)
Myocardial infarction	9 (3.6%)	9 (3.6%)	7 (2.8%)	18 (7.2%)	9 (3.6%)
Wound healing complications adverse events [b]	0	2 (0.8%)	6 (2.4%) [b]	3 (1.2%)	7 (2.8%) [c]

[a] Hypertension serious adverse events include hypertension, hypertensive crisis, and hypertensive emergency.

[b] Wound healing complication adverse events include open wound, postoperative wound infection, wound infection, and wound complication.

[c] One wound healing adverse event in the 0.5 mg group was reported as a serious adverse event.

Table 7 Extent of Study Drug Exposure

	Sham	0.3 mg Ranibizumab	0.5 mg Ranibizumab	Sham/0.5-mg Crossover (mo. 25–36)
24-month sham-controlled period				
Number of patients	250	250	250	NA
Number of injections [a]				
Total	5108	5242	5342	NA
Mean (SD)	20.4 (7.3)	21.0 (6.7)	21.4 (6.1)	NA
Median (min-max)	24 (1–25)	24 (1–25)	24 (1–25)	NA
Treatment duration (mo.)				
Mean (SD)	20.0 (7.3)	20.8 (6.6)	21.2 (6.1)	NA
Median (min-max)	23.7 (0–25)	23.7 (0–25)	23.7 (0–25)	NA
36-month study period				
Number of patients	NA	250	249 [b]	190
Number of ranibizumab injections				
Total	NA	7223	7327	1896
Mean (SD)	NA	28.9 (10.7)	29.4 (9.8)	10.0 (2.0)
Median (min-max)	NA	34 (1 – 36)	34 (1 – 36)	11 (1 – 13)
Treatment duration (mo.)				
Mean (SD)	NA	29.0 (10.6)	29.7 (9.9)	9.3 (1.9)
Median (min-max)	NA	34.5 (0–35)	34.5 (0–35)	9.8 (0–12)

[a] Note that sham patients did not receive a true intravitreal injection. Number of injections for sham patients represents number of times they received the sham procedure, which consisted of anesthetic and a syringe without a needle being placed against the eye.

[b] One sham patient received 0.5 mg ranibizumab starting at Month 23. This patient was classified in the 0.5-mg group for the 24-month analyses per the pre-specified definition of treatment groups for safety analyses. For the 36-month analyses, it was determined that this patient crossed over early and thus was classified in the sham/0.5-mg crossover group.

9.2.1 Ranibizumab Administration in the Fellow Eye

Fellow (non-study) eye treatment with ranibizumab was allowed following protocol amendments 3 and 4, respectively; thus, most of the fellow-eye treatment occurred in the third year of the study. Table 8 outlines the extent of exposure in the fellow eye for each of the 0.3-mg, 0.5-mg and sham/0.5-mg groups through 36 months.

Table 8 Ranibizumab Exposure in the Fellow Eye during the 36-Month Study Period

	0.3 mg Ranibizumab (n=250)	0.5 mg Ranibizumab (n=249)	Sham/0.5-mg Crossover (mo. 25–36) (n=190)
Patients treated in fellow eye, n	103	103	73 [a]
Number of injections			
Total	545	552	374
Mean (SD)	5.3 (3.6)	5.4 (3.5)	5.1 (3.1)
Median (min-max)	4 (1–15)	5 (1–14)	4 (1–12)
Treatment duration (mo)			
Mean (SD)	6.1 (4.0)	6.1 (4.2)	7.9 (2.6)
Median	6.8	6.5	8.9
Range	0–15	0–15	0–12

[a] Four additional patients received ranibizumab in the fellow eye before the crossover to 0.5 mg ranibizumab.

Dosing in the fellow eye was on an as-needed basis determined by the individual investigators and not on a mandated monthly dosing schedule. Therefore, the strength of any conclusions that can be drawn regarding the effect of increased exposure and AEs is limited by inconsistent exposure rates.

9.3 ADVERSE EVENTS

9.3.1 Ocular Adverse Events

Ocular AEs in RIDE and RISE were consistent with prior studies of ranibizumab, and events were those associated with the intravitreal injection procedure (e.g., conjunctival hemorrhage, vitreous floaters) or the underlying disease (e.g., maculopathy, retinal exudates). Table 9 presents common adverse events occurring at rates ≥5% and occurring with a frequency of ≥2% in the ranibizumab arms compared with sham during the 24-month sham-controlled treatment period.

Table 9 Common (≥5%) Ocular Adverse Events in the Study Eye with ≥2% Higher Frequency in Either Ranibizumab Group than Sham during the 24-Month Study Period

MedDRA Preferred Term	Sham (n=250)	0.3 mg Ranibizumab (n=250)	0.5 mg Ranibizumab (n=250)
Conjunctival hemorrhage	79 (31.6%)	118 (47.2%)	128 (51.2%)
Eye pain	32 (12.8%)	42 (16.8%)	43 (17.2%)
Retinal exudates	39 (15.6%)	44 (17.6%)	41 (16.4%)
Intraocular pressure increased	17 (6.8%)	44 (17.6%)	41 (16.4%)
Vitreous floaters	11 (4.4%)	25 (10.0%)	28 (11.2%)
Maculopathy	18 (7.2%)	13 (5.2%)	24 (9.6%)
Eye irritation	12 (4.8%)	20 (8.0%)	19 (7.6%)
Lacrimation increased	10 (4.0%)	13 (5.2%)	18 (7.2%)
Vision blurred	11 (4.4%)	21 (8.4%)	16 (6.4%)
Dry eye	8 (3.2%)	13 (5.2%)	13 (5.2%)
Foreign body sensation in eyes	12 (4.8%)	26 (10.4%)	12 (4.8%)

The rates of ocular AEs at Month 36 were similar to those at Month 24, and AE rates in the sham crossover group were comparable to the ranibizumab groups (Appendix 6, Table 6.1).

9.3.2 Ocular Serious Adverse Events

Table 10 presents the ocular SAEs occurring in ≥2 patients in any treatment group in the 24-month sham-controlled treatment period. The incidence of each reported ocular SAE was low (≤3 patients in any of the treatment groups) except for vitreous hemorrhage and reduced visual acuity, both of which occurred more frequently in the sham group. These specific SAEs may be associated with progression of underlying diabetic eye disease and were seen less frequently in ranibizumab-treated patients.

Table 10 Ocular Serious Adverse Events in the Study Eye Occurring in ≥ 2 Patients in Any Treatment Group during the 24-Month Controlled Treatment Period

MedDRA Preferred Term	Sham (n = 250)	0.3 mg Ranibizumab (n = 250)	0.5 mg Ranibizumab (n = 250)
Visual acuity reduced	4 (1.6%)	0	3 (1.2%)
Cataract	0	1 (0.4%)	2 (0.8%)
Cataract, traumatic	0	1 (0.4%)	2 (0.8%)
Endophthalmitis	0	2 (0.8%)	2 (0.8%)
Medication error	0	2 (0.8%)	2 (0.8%)
Vitreous hemorrhage	7 (2.8%)	0	2 (0.8%)
Macular edema	2 (0.8%)	0	0

Rates of ocular SAEs at Month 36 were similar to those at Month 24 and remained low for all treatment groups (Appendix 6, Table 6.2). The incidence of all ocular SAEs in all groups was below 2% with the exception of vitreous hemorrhage, which occurred in 3.6% of patients in the sham/0.5-mg group.

During 24 months of treatment, the per-injection rates of all ocular SAEs were low (< 0.05% per injection in each ranibizumab treatment group; Table 11), and consistent with per-injection rates seen in prior ranibizumab studies in AMD and RVO. Appendix 6, Table 6.3 shows the per-injection rates of selected ocular SAEs at Month 36.

Table 11 Per-Injection Rates of Selected Ocular Serious Adverse Events in the Study Eye during the 24-Month Controlled Treatment Period

MedDRA Preferred Term	Sham (n = 250)	Ranibizumab 0.3 mg (n =250)	Ranibizumab 0.5 mg (n =250)
Total number of injections	5108	5242	5342
Presumed endophthalmitis	0	2 (0.04%)	2 (0.04%)
Endophthalmitis	0	2 (0.04%)	2 (0.04%)
Cataract, traumatic	0	1 (0.02%)	2 (0.04%)
Retinal detachment	1 (0.02%)	0	1 (0.02%)
Intraocular inflammation	0	1 (0.02%)	0
Retinal tear	0	0	1 (0.02%)

Note: Presumed endophthalmitis included adverse events with endophthalmitis and intraocular inflammation, for which intravitreal or systemic antibiotics were administered. Intraocular inflammation included adverse events with MedDRA preferred term of uveitis.

9.3.3 Ocular Adverse Events Leading to Treatment Discontinuation

All ocular adverse events that led to treatment discontinuation through Month 24 are presented in Table 12. Events in the sham group occurring in ≥2 patients that contributed to discontinuation were those associated with worsening of the underlying diabetic eye disease (e.g., vitreous hemorrhage, macular edema), and more patients in the sham group discontinued treatment as a result of ocular AEs compared with the ranibizumab treatment groups. Only endophthalmitis occurred in ≥2 ranibizumab-treated patients leading to discontinuation.

Table 12 All Ocular Adverse Events in the Study Eye Leading to Treatment Discontinuation during the 24-Month Treatment Period

MedDRA Preferred Term	Sham (n=250)	0.3 mg Ranibizumab (n=250)	0.5 mg Ranibizumab (n=250)
- Any adverse events -	12 (4.8%)	1 (0.4%)	3 (1.2%)
Endophthalmitis	0	1 (0.4%)	1 (0.4%)
Diabetic retinal edema	2 (0.8%)	0	1 (0.4%)
Retinal neovascularization	0	0	1 (0.4%)
Vitreous adhesions	0	0	1 (0.4%)
Vitreous hemorrhage	4 (1.6%)	0	0
Macular edema	2 (0.8%)	0	0
Diabetic retinopathy	2 (0.8%)	0	0
Choroidal neovascularization	1 (0.4%)	0	0
Retinal aneurysm	1 (0.4%)	0	0
Retinal hemorrhage	1 (0.4%)	0	0
Dry eye	1 (0.4%)	0	0
Retinal detachment	1 (0.4%)	0	0

Ocular AEs in the study eye that led to treatment discontinuation during the 36-month treatment period are summarized in Appendix 6, Table 6.4.

9.3.4 Non-Ocular Adverse Events

The overall frequency of patients experiencing at least one non-ocular AE was similar across all treatment groups at 24 months (Table 6). Common non-ocular AEs (≥5% frequency in any treatment group) that occurred in the 0.3-mg and 0.5-mg groups at a ≥2% higher frequency in either ranibizumab treatment group than sham are shown in Table 13.

Table 13 Common (≥5%) Non-Ocular Adverse Events with ≥2% Higher Frequency in Either Ranibizumab Treatment Group than Sham during the 24-Month Controlled Treatment Period

MedDRA Preferred Term	Sham (n = 250)	0.3 mg Ranibizumab (n = 250)	0.5 mg Ranibizumab (n = 250)
Nasopharyngitis	15 (6.0%)	29 (11.6%)	25 (10.0%)
Cough	11 (4.4%)	23 (9.2%)	16 (6.4%)
Constipation	10 (4.0%)	19 (7.6%)	14 (5.6%)
Seasonal allergy	9 (3.6%)	19 (7.6%)	9 (3.6%)
Influenza	7 (2.8%)	18 (7.2%)	19 (7.6%)
Hypercholesterolemia	12 (4.8%)	18 (7.2%)	9 (3.6%)
Gastroesophageal reflux disease	11 (4.4%)	16 (6.4%)	15 (6.0%)
Edema, peripheral	11 (4.4%)	16 (6.4%)	11 (4.4%)
Cardiac failure, congestive	12 (4.8%)	10 (4.0%)	17 (6.8%)
Renal failure, chronic	4 (1.6%)	14 (5.6%)	13 (5.2%)
Neuropathy, peripheral	8 (3.2%)	13 (5.2%)	8 (3.2%)
Coronary artery disease	6 (2.4%)	11 (4.4%)	14 (5.6%)
Diarrhea	11 (4.4%)	9 (3.6%)	22 (8.8%)

Direct comparisons between the sham/0.5-mg and ranibizumab groups at Month 36 may be misleading, as there was no sham control group at the 36-month timepoint. Month 36 event rates for the most common non-ocular AEs in the ranibizumab groups were generally similar to the Month 24 rates and/or consistent with the expected higher rates based on an additional year of observation (Appendix 6, Table 6.5).

9.3.5 Non-Ocular Serious Adverse Events

Non-ocular SAEs with ≥1% higher frequency in either ranibizumab treatment group than sham during the 24-month controlled period are shown in Table 14. In general, higher rates were observed in the ranibizumab-treated groups than in the sham group.

Table 14 Non-Ocular Serious Adverse Events with ≥1% Higher Frequency in Either Ranibizumab Treatment Group than Sham during the 24-Month Controlled Treatment Period

MedDRA Preferred Term [a]	Sham (n=250)	0.3 mg Ranibizumab (n=250)	0.5 mg Ranibizumab (n=250)
Coronary artery disease	2 (0.8%)	6 (2.4%)	7 (2.8%)
Cerebrovascular accident	3 (1.2%)	3 (1.2%)	7 (2.8%)
Hypertension	1 (0.4%)	3 (1.2%)	6 (2.4%)
Renal failure	4 (1.6%)	8 (3.2%)	5 (2.0%)
Acute myocardial infarction	0	4 (1.6%)	3 (1.2%)
Renal failure, chronic	0	4 (1.6%)	2 (0.8%)
Respiratory failure	0	3 (1.2%)	2 (0.8%)
Pneumonia	7 (2.8%)	4 (1.6%)	10 (4.0%)

[a] Related serious adverse event preferred terms that did not meet the criteria of ≥1% higher frequency are not included in this table (e.g., myocardial infarction).

At Month 36, the frequency of non-ocular SAEs in the 0.3-mg and 0.5-mg ranibizumab groups (Appendix 6, Table 6.6) was generally comparable to those seen at Month 24, with expected higher rates based on the additional year of observation.

9.4 NON-OCULAR ADVERSE EVENTS LEADING TO TREATMENT DISCONTINUATION

Table 15 presents the non-ocular adverse events leading to treatment discontinuation occurring in >2 patients in any treatment group through 24 months.

Table 15 Non-Ocular Adverse Events Leading to Treatment Discontinuation in ≥2 Patients in Any Treatment Group during the 24-Month Controlled Treatment Period

MedDRA Preferred Term [a]	Sham (n=250)	0.3 mg Ranibizumab (n=250)	0.5 mg Ranibizumab (n=250)
Cardiac arrest	1 (0.4%)	1 (0.4%)	2 (0.8%)
Cerebrovascular accident	1 (0.4%)	2 (0.8%)	2 (0.8%)
Renal failure	2 (0.8%)	0	1 (0.4%)
Respiratory failure	0	2 (0.8%)	0

[a] Related adverse events leading to treatment discontinuation that did not occur in ≥2 patients in any treatment group are not included in this table (e.g. acute renal failure).

At 36 months, 19 (7.6%) patients in the 0.5-mg group and 20 (8.0%) patients in the 0.3-mg group discontinued treatment because of non-ocular AEs (Table 6). Rates of individual events leading to discontinuation were low in each individual category of

events and similar across categories of events at both Month 24 and Month 36 (Appendix 6, Table 6.7).

9.5 ANTI-VEGF RELATED ADVERSE EVENTS

To further assess the safety of ranibizumab in the treatment of DME, non-ocular adverse events of particular interest were further analyzed using three different approaches: 1) the Antiplatelet Trialists' Collaboration (APTC) classification of arteriothromboembolic events (ATEs); 2) AEs potentially related to systemic inhibition of VEGF; and 3) adverse events of special interest (AESI). These three approaches are described below.

- APTC classification: The analysis of ATEs was performed using the APTC classification, which is based on a specific and well-defined spectrum of ATE AEs: vascular deaths (including deaths of unknown cause), non-fatal myocardial infarction, and non-fatal stroke (Antiplatelet Trialists' Collaboration 1994). The analysis of APTC ATEs is presented in Section 9.5.1.
- Adverse events potentially related to systemic VEGF inhibition: In previous studies of intravitreal ranibizumab, Genentech had reported a set of AEs historically associated with systemic VEGF inhibition. These AEs, based on verbatim reporting, include ATEs, hypertension, non-ocular hemorrhage, and proteinuria—a broader list of AEs than the APTC classification. Currently, the classification of adverse events potentially related to systemic VEGF inhibition has been replaced by adverse events of special interest.
- Adverse events of special interest: Through the safety surveillance system in place for systemic bevacizumab, additional categories of systemic AEs have recently been identified based on use with intravenous anti-VEGF treatment for oncology indications. These systemic AEs, broadly categorized as adverse events of special interest (AESI), were identified using two methodologies: 1) standardized MedDRA Queries (SMQs) for the specific AESI terms and 2) groups of AEs identified from the clinical experience with systemic bevacizumab. This approach provides an even broader categorization of AEs than either the APTC classification or the AEs potentially related to systemic VEGF inhibition. The analysis of AESIs is presented in Section 9.5.2 and in Appendix 6, Tables 6.8 and 6.9.

Because these classification systems use different preferred and/or grouped terms, variability in the event rates will emerge depending on the method used. These differences will be highlighted and addressed where applicable in the following sections.

9.5.1 Antiplatelet Trialists' Collaboration Events: Myocardial Infarctions, Strokes, and Deaths

The incidence of APTC-classified MIs, strokes, and deaths during the 24-month and 36-month study periods is shown in Table 16 and Table 17, respectively.

At Month 24, a numerical trend toward a dose-dependent, higher incidence of overall APTC ATEs was observed for the ranibizumab-treated groups compared with the sham groups. This imbalance was driven primarily by trends for death (all-cause, vascular,

and non-vascular) and stroke. In contrast, the incidence of MI was similar across the three treatment groups.

Because most of the sham patients crossed over to receive 0.5 mg ranibizumab in the third year of treatment, events that occurred in the sham/0.5-mg group after crossover make the interpretation of Month 36 rates difficult. At Month 36, consistent with the Month 24 data, a higher number of deaths and strokes were observed in the 0.5-mg dose group compared with the 0.3-mg dose group (Table 17). In contrast, the 0.5-mg group had a lower number of MIs than the 0.3-mg group.

Table 16 Deaths, Myocardial Infarctions, and Stroke during the 24-Month Controlled-Treatment Period

Event Type	Sham (n=250)	0.3 mg Ranibizumab (n=250)	0.5 mg Ranibizumab (n=250)
Any event	13 (5.2%)	16 (6.4%)	22 (8.8%)
Deaths	3 (1.2%)	7 (2.8%)	11 (4.4%)
Vascular	3 (1.2%)	5 (2.0%)	6 (2.4%)
Non-vascular	0	2 (0.8%)	4 (1.6%)
Unknown cause	0	0	1 (0.4%)
Myocardial infarction	9 (3.6%)	9 (3.6%)	7 (2.8%)
Fatal	2 (0.8%)	2 (0.8%)	1 (0.4%)
Non-fatal	7 (2.8%)	7 (2.8%)	6 (2.4%)
Stroke (cerebrovascular accident)	4 (1.6%)	3 (1.2%)	8 (3.2%)
Fatal	1 (0.4%)	1 (0.4%)	3 (1.2%)
Non-fatal	3 (1.2%)	2 (0.8%)	5 (2.0%
APTC-classified events [a]	13 (5.2%)	14 (5.6%)	18 (7.2%)

[a] APTC=Antiplatelet Trialists' Collaboration. Events include vascular deaths, unknown cause deaths, non-fatal MIs, and non-fatal strokes.

Table 17 Deaths, Myocardial Infarctions, and Stroke during the 36-Month Study Period

Event Type	Sham Month 0–24 (n=250)	Sham/ 0.5 mg [a] Month 0–36 (n=251)	0.3 mg RBZ Month 0–36 (n=250)	0.5 mg RBZ Month 0–36 (n=249) [b]
Any event	13 (5.2%)	20 (8.0%)	29 (11.6%)	33 (13.3%)
Deaths	3 (1.2%)	7 (2.8%)	11 (4.4%)	16 (6.4%)
Vascular	3 (1.2%)	5 (2.0%)	8 (3.2%)	8 (3.2%)
Non-vascular	0 (0.0%)	2 (0.8%)	2 (0.8%)	7 (2.8%)
Unknown cause	0 (0.0%)	0 (0.0%)	1 (0.4%)	1 (0.4%)
Myocardial infarction	9 (3.6%)	13 (5.2%)	18 (7.2%)	9 (3.6%)
Fatal	2 (0.8%)	4 (1.6%)	3 (1.2%)	1 (0.4%)
Non-fatal	7 (2.8%)	9 (3.6%)	15 (6.0%)	8 (3.2%)
Stroke (cerebrovascular accident)	4 (1.6%)	6 (2.4%)	5 (2.0%)	12 (4.8%)
Fatal	1 (0.4%)	2 (0.8%)	1 (0.4%)	3 (1.2%)
Non-fatal	3 (1.2%)	4 (1.6%)	4 (1.6%)	9 (3.6%)
APTC-classified events [c]	13 (5.2%)	18 (7.2%)	27 (10.8%)	26 (10.4%)

RBZ = ranibizumab. Counts represent number of patients reporting the event. There is no pure sham control group at Month 36 so it is not valid to compare the sham groups with the ranibizumab treatment arms.

[a] Patients initially randomized to sham including those who crossed over to 0.5 mg ranibizumab during Year 3.

[b] One sham patient received 0.5 mg ranibizumab starting at Month 23. This patient was classified in the 0.5-mg group for the 24-month analyses per the pre-specified definition of treatment groups for safety analyses. For the 36-month analyses, it was determined that this patient crossed over early and thus was classified in the sham/0.5-mg crossover group.

[c] APTC = Antiplatelet Trialists' Collaboration. Events include vascular deaths, unknown cause deaths, non-fatal MIs, and non-fatal strokes

To explore whether increased exposure to intravitreal ranibizumab was associated with higher rates of APTC ATEs, events for patients who received unilateral versus bilateral treatment during Months 25–36 were tabulated; most patients initiated bilateral treatment after Month 24 (Table 18). This approach is limited because the subgroups were defined by post-randomization characteristics, the two groups may not have matched baseline characteristics, and fellow eye treatment with 0.5 mg ranibizumab was on an as-needed basis and not on a monthly dosing schedule. The RIDE and RISE studies were not designed to investigate the safety of bilateral dosing, and a definitive conclusion cannot be drawn. Nevertheless, this tabulation did not appear to show a systematic difference in event rates in patients receiving bilateral injections.

Table 18 Cumulative Ranibizumab Exposure and APTC Events during Months 25–36 by Dosing Group

	0.3 mg RBZ Unilateral [a] (n=96)	0.5 mg RBZ Unilateral [a] (n=105)	0.3 mg RBZ Bilateral [b] (n=102)	0.5 mg RBZ Bilateral [b] (n=100)
Total dose (mg) of ranibizumab received during Months 25–36				
Mean (SD)	2.9 (0.7)	4.8 (1.1)	5.6 (1.9)	7.6 (2.0)
Median	3.3	5.5	5.3	7.5
Range (min–max)	0.3–5.5	0.5–5.5	1.4–8.8	3.0–11.0
APTC events during Months 25–36, n (%)				
All deaths	4 (4.2%)	4 (3.8%)	0	1 (1.0%)
Vascular deaths	3 (3.1%)	2 (1.9%)	0	0
Stroke	2 (2.1%)	1 (1.0%)	0	1 (1.0%)
MI	4 (4.2%)	0	5 (4.9%)	2 (2.0%)
Event rate per 100 patient years				
All deaths	4.4	4.0	0	1.3
Vascular deaths	3.3	2.0	0	0
Stroke	2.2	1.0	0	1.3
MI	4.5	0.0	6.5	2.7

APTC events=Antiplatelet Trialists' Collaboration; events include vascular deaths, unknown cause deaths, non-fatal MIs, non-fatal cerebrovascular accidents (CVAs); MI=myocardial infarction; RBZ=ranibizumab.

[a] Unilateral means the patient did not receive any ranibizumab in the fellow eye during Months 25–36; bilateral means the patient received at least one dose of 0.5 mg ranibizumab in the fellow eye during Months 25–36.

[b] For bilateral groups, the ranibizumab dose includes injections received in both the study eye (0.3 and 0.5-mg groups) and fellow eye (0.5-mg) during Months 25–36. Events that occurred prior to the initiation of bilateral treatment were excluded from the summary.

Further assessment of the data on APTC ATEs associated with ranibizumab use in DME was performed to explore the differences in stroke, death, and MI, between treatment groups. These analyses are inherently limited by the small number of events and are provided for descriptive purposes only. These analyses included:

- Kaplan-Meier curves for the time to first occurrence of each event to evaluate the treatment effect on the risk of event. In most cases, each vertical step of the Kaplan–Meier curve represents one event.
- Cox regression analysis at Months 24 and 36 to evaluate whether differences between treatment groups remained after adjustment for potential baseline risk factors associated with the events and whether any baseline risk factors could be predictive of event occurrence. Appendix 7 provides additional details of the Cox regression analysis.

- A review of the published literature on the rates of systemic events in DME patients involved in other clinical studies of ranibizumab: the Diabetic Retinopathy Clinical Research Network (DRCR.net) Protocol I, a randomized trial of ranibizumab in DME (DRCR.net 2010; Elman et al. 2011), and RESTORE, a registrational study conducted by Novartis outside the U.S. (Mitchell et al. 2011), were reviewed to provide additional comparative clinical trial data in the DME patient population. Both of these studies utilized less than monthly dosing regimens, which constitutes an important difference in exposure to ranibizumab from the RIDE and RISE monthly dosing schedule. See Section 3.2 for detailed descriptions of these two trials.

9.5.1.1 Strokes

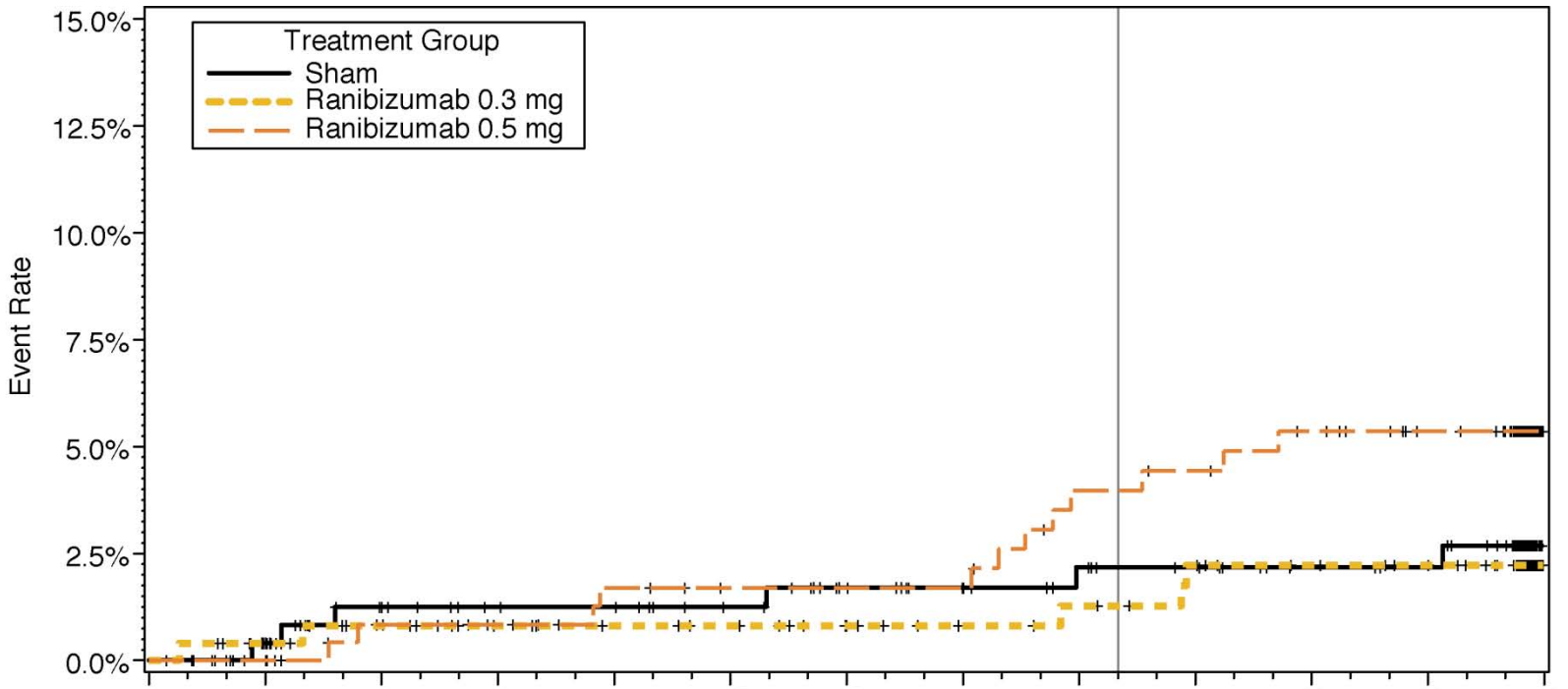
Strokes included events reported as the following MedDRA AE preferred terms: cerebrovascular accident, lacunar infarction, ischemic stroke, cerebral hemorrhage, cerebellar infarction, and cerebral infarction.

The Kaplan-Meier curve presented in Figure 28 shows that the risk of stroke was similar across the three treatment groups until Month 21. After Month 21, the rate of stroke was higher in the 0.5-mg group. Cox regression analysis did not identify baseline risk factors associated with risk of stroke at Month 24 and 36 that accounted for the imbalance in stroke rates between the treatment groups (Appendix 7, Table 7.1).

By comparison, the number of strokes in the DRCR.net Protocol I study was 5 (4%) in the sham group and 3 (1%) in the ranibizumab group at 1 year (DRCR.net 2010). In Year 2, 8 (6%) strokes had occurred in the sham group and 7 (2%) in the ranibizumab group. The number of strokes reported in RESTORE at 1 year were 1 (<1%) in the 0.5-mg group, 0 in ranibizumab plus laser group, and 0 in the laser only group (Mitchell et al. 2011). Patients with a prior history of stroke were excluded from this trial. Both studies employed less than monthly dosing regimens.

In aggregate, the trend toward a higher rate of stroke events in the 0.5-mg group at Month 24 and 36, the demonstration of a similar numerical trend in other ranibizumab indications, and the biologic plausibility of VEGF inhibition causality for stroke suggest that a potential risk of increased stroke rate with ranibizumab treatment cannot be excluded.

Figure 28 Kaplan-Meier Estimated Rate of Stroke during the 36-Month Study Period



Number at risk

Sham	251	243	231	224	223	217	212	210	206	202	196	193	11
Ranibizumab 0.3 mg	250	245	235	229	226	224	219	214	212	208	204	201	12
Ranibizumab 0.5 mg	249	244	236	233	228	225	222	218	210	208	204	197	18

Patients in the control (sham) group who did not discontinue from treatment were eligible to participate in the crossover plan and receive 0.5 mg ranibizumab starting at Month 25 for the remainder of the treatment period. In this figure, the two sham groups (sham only and sham/0.5-mg) are combined, and a line representing the start of the crossover plan is shown. A few sham patients crossed over early (Month 23) per treatment criteria.

9.5.1.2 All Deaths

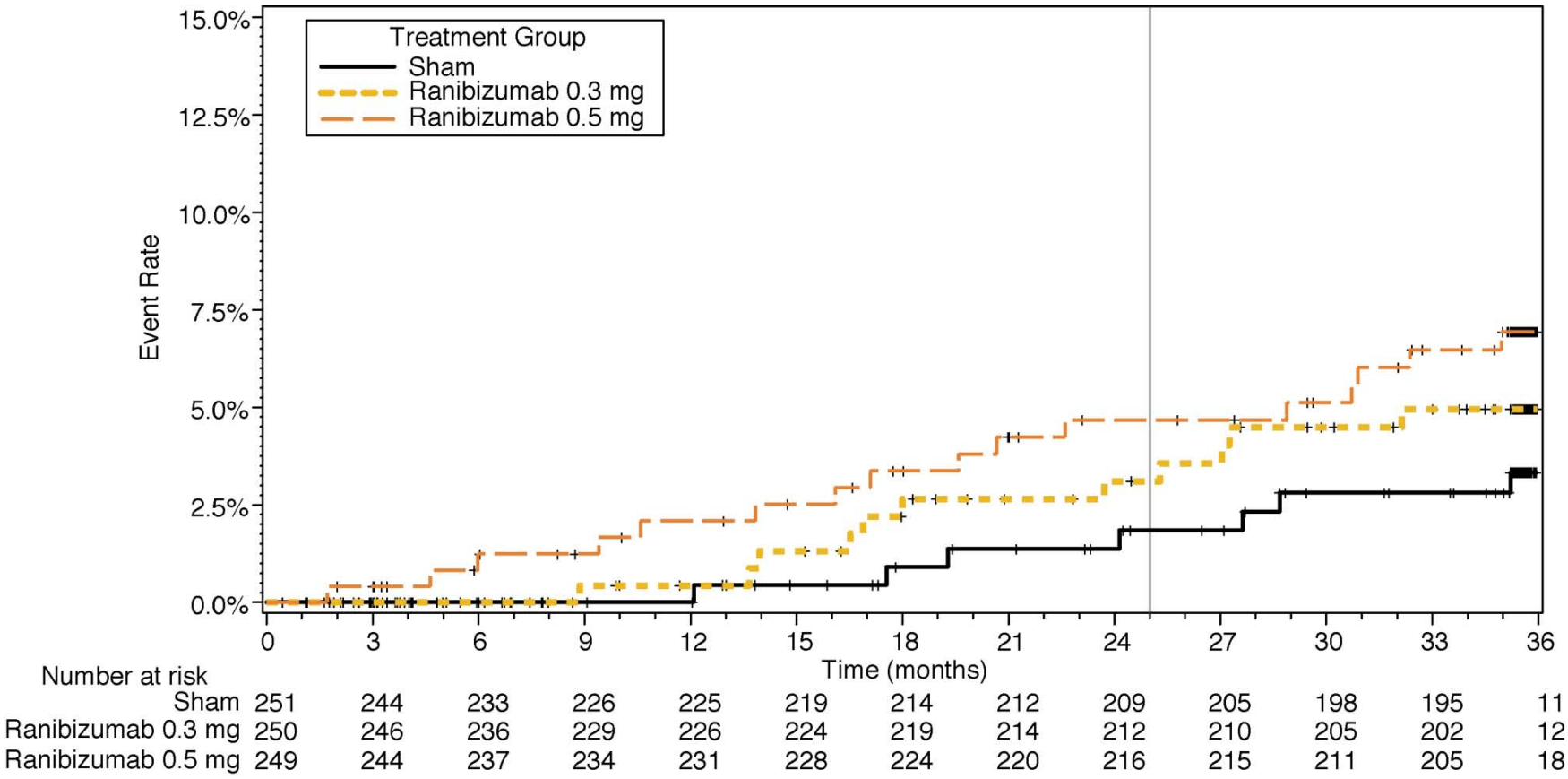
The Kaplan-Meier curve presented in Figure 29 shows that a higher risk of death was observed persistently over time beginning at Month 2 and continuing through Month 36 in the 0.5-mg group compared with the 0.3-mg and sham/0.5-mg groups. A higher risk was also observed in the 0.3-mg group compared with the sham/0.5-mg group, with separation of curves starting after 12 months of treatment. The difference between the 0.3-mg and 0.5-mg groups was the result of more non-vascular deaths in the 0.5-mg group: 7 (2.8%) compared with 2 (0.8%) in the 0.3-mg group observed at Month 36.

The Cox regression analyses did not identify baseline risk factors that were predictive of death at Month 24 and Month 36 that could account for the imbalance in mortality between dose groups (Appendix 7, Table 7.1).

By comparison, in the DRCR.net Protocol I study, the number of total deaths was 4 (3%) in the sham group and 8 (2%) in the ranibizumab (0.5-mg) group at 1 year. The number of total deaths at 2 years was 15 (11.5%) in the sham group and 15 (4%) in the ranibizumab group. Event rates of vascular deaths were 4 (3%) in the sham group and 7 (2%) in the ranibizumab group at 1 year, and 8 (6%) in the sham group, and 13 (3%) in the ranibizumab group at 2 years (DRCR.net 2010; Elman et al. 2011). In RESTORE at Year 1, event rates of death were 2 (1.8%) in the sham group and 4 (1.7%) in the ranibizumab group (Mitchell et al. 2011). Both studies employed less than monthly dosing regimens.

Appendix 6, Table 6.10 lists the causes of death by treatment group including patient age, gender, date of death, number of injections, and time from last study treatment. Although causes of death were typical of patients with advanced diabetic complications, the trend toward a dose-dependent higher rate of deaths in the ranibizumab groups at Month 24 and 36 suggest that a potential risk of increased death with ranibizumab treatment cannot be excluded.

Figure 29 Kaplan-Meier Estimated Rate of Patient Deaths during the 36-Month Study Period



Patients in the control (sham) group who did not discontinue from treatment were eligible to participate in the crossover plan and receive 0.5 mg ranibizumab starting at Month 25 for the remainder of the treatment period. In this figure, the two sham groups (sham only and sham/0.5-mg) are combined, and a line representing the start of the crossover plan is shown. A few sham patients crossed over early (Month 23) per treatment criteria.

9.5.1.3 Myocardial Infarctions

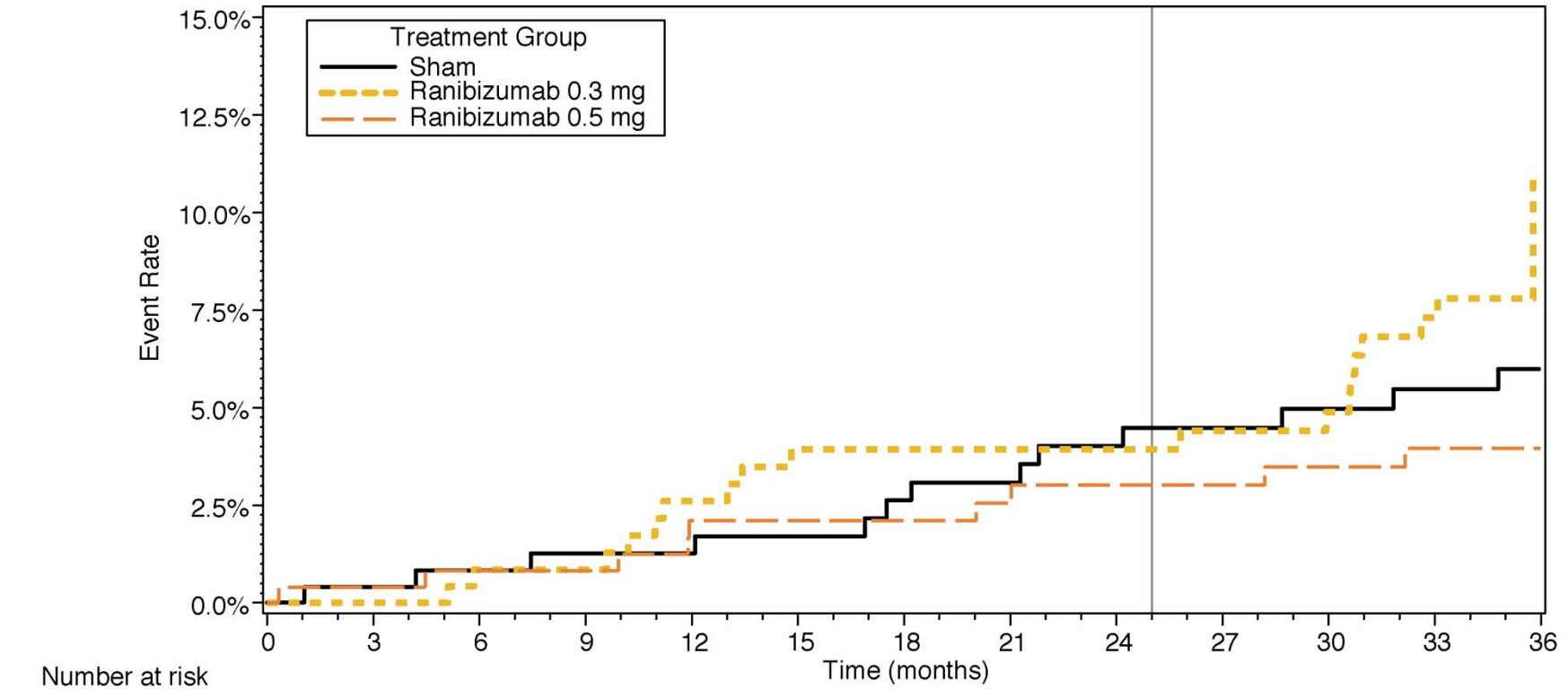
The Kaplan-Meier curve shows that the rate of MI was similar across all three treatment groups until Month 30 (Figure 30). Seven MIs occurred in patients in the 0.3-mg group after Month 30 and resulted in a higher MI rate in this group, compared with the sham/0.5-mg group and the 0.5-mg group.

Given that there was no imbalance in MI rates at Month 24 (Table 17), Cox regression analysis was not performed for this timepoint. The Cox regression analyses at Month 36 did not identify baseline risk factors that could account for the imbalance in myocardial infarction rates between dose groups (Appendix 7, Table 7.1).

By comparison, MI in the DRCR.net Protocol I study occurred in 1 (<1%) patient in the ranibizumab group, and 3 (2%) patients in the sham group at Year 1 (DRCR.net 2010). At Year 2, there were 4 (3%) MIs in the sham group and 5 (1%) MIs in the ranibizumab groups (Elman et al. 2011). In RESTORE at 1 year, MI occurred in 1 (<1%) patient in the ranibizumab group, 1 (<1%) patient in the ranibizumab/laser group, and 0 patients in the laser monotherapy group (Mitchell et al. 2011). Both studies employed less than monthly dosing regimens with overall less exposure to ranibizumab than that in RIDE and RISE.

In aggregate, these data do not suggest a causal relationship between ranibizumab treatment and MI in DME patients.

Figure 30 Kaplan-Meier Estimated Rate of Myocardial Infarction during the 36-Month Study Period



Patients in the control (sham) group who did not discontinue from treatment were eligible to participate in the crossover plan and receive 0.5 mg ranibizumab starting at Month 25 for the remainder of the treatment period. In this figure, the two sham groups (sham only and sham/0.5-mg) are combined, and a line representing the start of the crossover plan is shown. A few sham patients crossed over early (Month 23) per treatment criteria.

9.5.2 Adverse Events of Special Interest

To characterize any additional adverse events of special interest (AESI) potentially linked to systemic VEGF inhibition in RIDE and RISE, the study databases were queried to identify AEs and SAEs falling into the following special interest categories:

- CNS and cerebrovascular hemorrhage
- Non-CNS hemorrhage
- Congestive heart failure
- Fistulae
- Gastrointestinal perforation
- Hypertension
- Proteinuria
- Venous thromboembolic events
- Arterial thromboembolic events
- Wound healing complications

The results of the AESI analyses are shown in Table 19 and Table 20. Overall, the incidence of AESI adverse events at Month 24 was balanced between treatment groups, though differences in important individual event categories were noted (Table 19). The incidence of AESI serious adverse events was numerically higher in the 0.5 mg ranibizumab group (Table 20).

Table 19 Non-Ocular Adverse Events of Special Interest during the 24-Month Treatment Period

AE Group Term	Sham (n=250)	0.3 mg Ranibizumab (n=250)	0.5 mg Ranibizumab (n=250)
Any non-ocular AESI	89 (35.6%)	78 (31.2%)	93 (37.2%)
Any bleeding/hemorrhage adverse event	12 (4.8%)	14 (5.6%)	20 (8.0%)
Bleeding/hemorrhage (CNS and cerebrovascular hemorrhage)	3 (1.2%)	3 (1.2%)	7 (2.8%)
Bleeding/hemorrhage (non-CNS hemorrhage)	9 (3.6%)	12 (4.8%)	14 (5.6%)
Congestive heart failure	15 (6.0%)	11 (4.4%)	20 (8.0%)
Fistulae (other)	0	2 (0.8%)	1 (0.4%)
Gastrointestinal perforation	0	1 (0.4%)	1 (0.4%)
Hypertension	51 (20.4%)	48 (19.2%)	56 (22.4%)
Proteinuria	11 (4.4%)	10 (4.0%)	9 (3.6%)
Thromboembolic event, arterial	20 (8.0%)	18 (7.2%)	23 (9.2%)
Thromboembolic event, venous	1 (0.4%)	6 (2.4%)	2 (0.8%)
Wound healing complications	0	2 (0.8%)	6 (2.4%)

AESI=adverse events of special interest.

Table 20 Non-Ocular Serious Adverse Events of Special Interest during the 24-Month Treatment Period

AE Group Term	Sham (n=250)	0.3 mg Ranibizumab (n=250)	0.5 mg Ranibizumab (n=250)
Any non-ocular AESI	29 (11.6%)	27 (10.8%)	34 (13.6%)
Any bleeding/hemorrhage adverse event	7 (2.8%)	7 (2.8%)	8 (3.2%)
Bleeding/hemorrhage (CNS and cerebrovascular hemorrhage)	3 (1.2%)	3 (1.2%)	7 (2.8%)
Bleeding/hemorrhage (non-CNS hemorrhage)	4 (1.6%)	4 (1.6%)	2 (0.8%)
Congestive heart failure	11 (4.4%)	7 (2.8%)	10 (4.0%)
Fistulae (other)	0	1 (0.4%)	0
Gastrointestinal perforation	0	0	1 (0.4%)
Hypertension	1 (0.4%)	3 (1.2%)	6 (2.4%)
Proteinuria	0	0	1 (0.4%)
Thromboembolic event, arterial	17 (6.8%)	14 (5.6%)	20 (8.0%)
Thromboembolic event, venous	1 (0.4%)	4 (1.6%)	2 (0.8%)
Wound healing complications	0	0	1 (0.4%)

AESI=adverse events of special interest.

The AESI AEs and SAEs at 36 months are presented in Appendix 6, Tables 6.8 and 6.9.

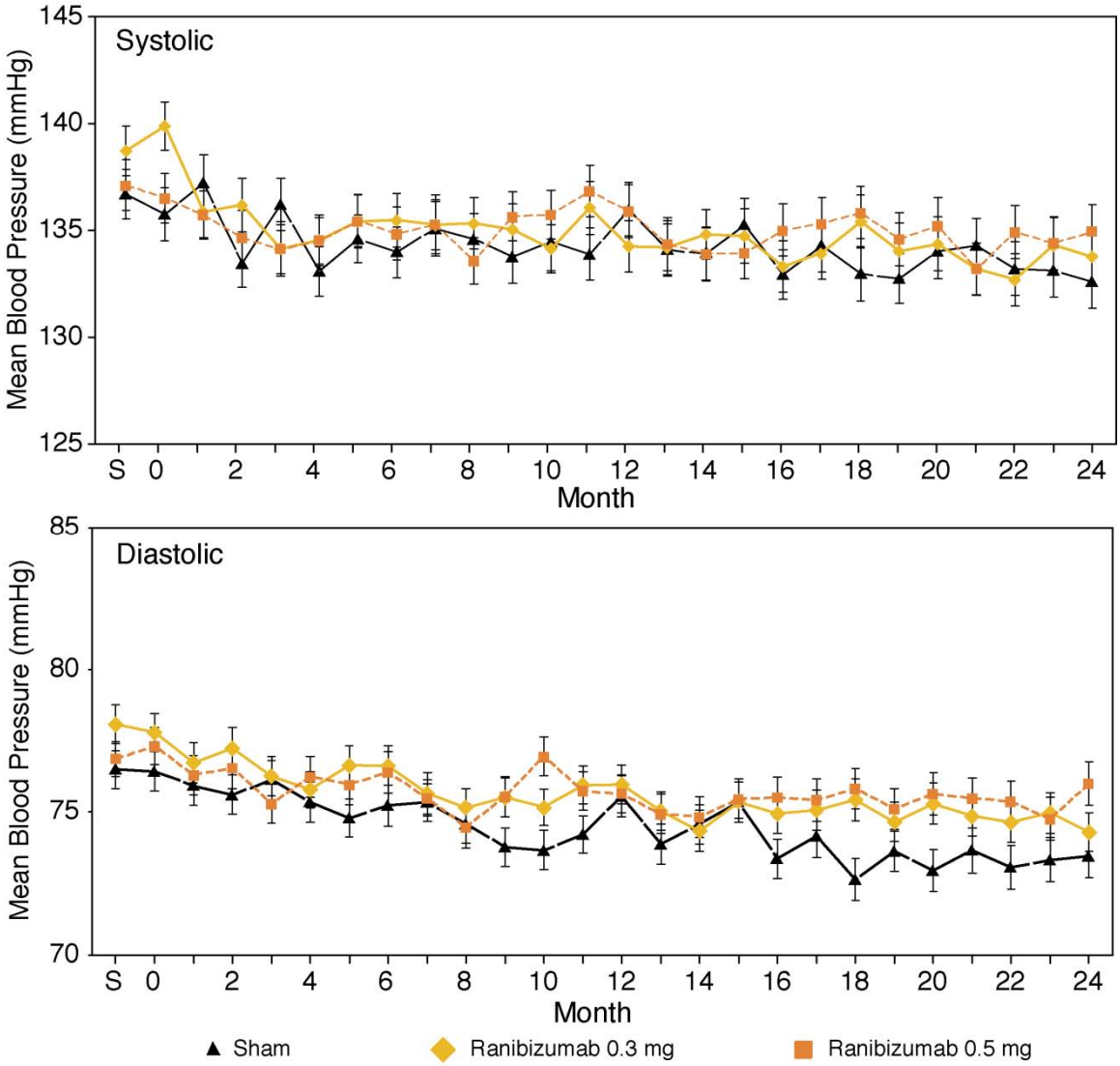
9.5.2.1 Hypertension

The AESI analysis of hypertension identified the following preferred terms reported as AEs: accelerated hypertension, blood pressure inadequately controlled, blood pressure increased, hypertension, hypertensive crisis, hypertensive emergency, hypertensive encephalopathy, labile blood pressure, malignant hypertension, metabolic syndrome, and orthostatic hypertension. At Month 24 the rates of hypertension reported as an AE were numerically higher in the 0.5-mg group at 56 (22.4%), compared with 48 (19.2%) in the 0.3 mg group and 51 (20.4%) in the sham group (Table 19). The AESI analysis of hypertension reported as an SAE identified the preferred terms of hypertension, hypertensive crisis, and hypertensive emergency in the AESI grouping. The analysis showed a trend toward a dose-dependent, numerically higher SAE rate in ranibizumab-treated groups than in sham groups: 1 (0.4%) in the sham group, 3 (1.2%) in the 0.3-mg group, and 6 (2.4%) in the 0.5-mg group, respectively (Table 20).

Analyses were performed on blood pressure over time by treatment group to determine whether the higher incidence of hypertension SAEs in ranibizumab-treated groups indicated a systematic elevation in blood pressure in association with ranibizumab treatment. Overall, the mean blood pressure tended to decline over time in all treatment groups, with no evidence of elevation in the ranibizumab-treated groups (Figure 31).

In aggregate, the trend toward a dose-dependent increase in hypertension SAEs, the trend toward a higher rate of hypertension adverse events in the 0.5-mg group, and the biologic plausibility of VEGF inhibition causality for hypertension suggest that a potential risk of increased hypertension rates with ranibizumab treatment cannot be excluded.

Figure 31 Mean Blood Pressure over Time by Treatment Group



S=screening. Vertical bars are ±1 standard error of the mean. On days of injection, blood pressure was taken prior to the injection. This summary excludes blood pressure assessments after early crossover to ranibizumab for patients in the sham group.

9.5.2.2 Wound Healing Complications

Wound healing complications included adverse event preferred terms of open wound, post-operative wound infection, wound infection, and wound complication. The AESI analysis at 24 months demonstrated a greater number of wound healing AEs reported in the 0.5-mg group (2.4%) compared with the 0.3-mg group (0.8%) and sham group (0%). Similarly, at 36 months, a greater number of wound healing AEs were reported in patients receiving 0.5 mg ranibizumab 7 (2.8%) than 0.3 mg ranibizumab 3 (1.2%) or sham/0.5-mg 0 (0%) (Appendix 6, Table 6.8). One event that occurred in 1 patient in the 0.5-mg group was reported as serious.

The trend toward a dose-dependent relationship and the known association of wound healing complications with systemic VEGF inhibition suggest that causality of ranibizumab treatment in the impairment of wound healing in DME patients cannot be excluded. This finding may be particularly relevant in DME patients because of the background impairment of wound healing as a consequence of chronic diabetes.

9.5.2.3 Relevant Nonclinical Toxicology Reproductive Information

A comprehensive safety evaluation of ranibizumab following intravitreal injections of up to 2.0 mg/eye of ranibizumab every 2 weeks for up to 26 weeks was conducted in cynomolgus monkeys. A dose-dependent intraocular inflammation was observed that has not been representative of effects seen in humans and may, in part, be related to immunogenicity in monkeys. In addition, no systemic toxicity was observed in monkeys following intravitreal injections of ranibizumab.

An embryo-fetal developmental toxicity study was performed on pregnant cynomolgus monkeys. Pregnant animals received intravitreal injections of ranibizumab every 14 days starting on Day 20 of gestation, until Day 62 at doses of 0, 0.125, and 1 mg/eye. Skeletal abnormalities including incomplete and/or irregular ossification of bones in the skull, vertebral column, and hindlimbs and shortened supernumerary ribs were seen at a low incidence in fetuses from animals treated with 1 mg/eye of ranibizumab. The 1 mg/eye dose resulted in trough serum ranibizumab levels up to 13 times higher than predicted maximum concentration (C_{max}) levels with single-eye treatment in humans. No skeletal abnormalities were seen at the lower dose of 0.125 mg/eye, a dose which resulted in trough exposures equivalent to single-eye treatment in humans. No effect on the weight or structure of the placenta, maternal toxicity, or embryotoxicity was observed.

It is not known whether ranibizumab can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Animal reproduction studies are not always predictive of human response; however, based on the anti-VEGF mechanism of action for ranibizumab, treatment with ranibizumab may pose a risk to embryo-fetal development (including teratogenicity) and reproductive capacity. Because of the concerns for the developing fetus, pregnant women were excluded from enrollment in RIDE and RISE trials. However, some women with DME may be of reproductive age or be pregnant. Therefore, ranibizumab should be given to a pregnant woman only if clearly needed.

Proposed labeling describing these reproductive toxicology findings and their relevance to the use of ranibizumab during pregnancy are currently under review by FDA under a separate regulatory submission.

9.6 SAFETY CONCLUSIONS

Ranibizumab was generally well-tolerated in DME patients through 36 months, with a safety profile similar to the established profile of ranibizumab in patients with neovascular AMD and macular edema following RVO. The most common ocular

adverse events reported more frequently in ranibizumab-treated DME patients than sham group patients were those primarily related to the intravitreal injection procedure; rates of key ocular serious adverse events were low with a per-injection rate of procedure-related AEs consistent with other large Phase III studies of ranibizumab across several disease indications.

Patients in the sham group experienced a greater number of ocular adverse events related to worsening of their underlying diabetic retinopathy.

Systemically, the observed types and rates of adverse events were as expected in patients with advanced diabetic complications, and safety events, which occurred at low but higher rates in ranibizumab-treated patients were in categories known or potentially related to systemic VEGF inhibition. Myocardial infarction occurred at a higher rate in the 0.3-mg group compared with the 0.5-mg or sham groups. Stroke, all-cause mortality, serious events of hypertension, and adverse events related to wound healing occurred at higher rates in the 0.5-mg group compared with the 0.3-mg or sham groups.

10. BENEFIT–RISK PROFILE

Diabetes is the leading cause of new cases of blindness in working-aged Americans. Most vision loss from diabetes results from DME and proliferative diabetic retinopathy. Although retinal laser treatments can reduce the risk of subsequent vision loss in patients with diabetes who develop these complications, relatively few patients with DME treated with retinal laser will experience improvements in visual acuity, and the vision gains that do occur are typically modest. Additionally, 10%–15% of patients with DME treated with macular laser will nevertheless experience substantial (≥15 letter) vision loss over the subsequent 2 years; this rate has remained consistent across studies for the past quarter-century since the advent of ETDRS-style macular laser. To date, there are no FDA-approved medical treatments that substantively improve vision in patients with DME; treatment of vision loss from DME thus remains an important area of unmet medical need. Given the importance of vision preservation and restoration to patients (Brown et al. 1999; Brown et al. 2001), a therapy that could improve visual acuity in patients with diabetes who have lost vision from DME, while also preventing additional vision loss and retarding further worsening of the underlying retinopathy with an acceptable safety profile, would greatly benefit patients affected by DME, their families, and society.

10.1 BENEFITS OF RANIBIZUMAB IN DME

In RIDE and RISE, intravitreal ranibizumab demonstrated robust and clinically important efficacy in patients with DME when compared with sham injections (with macular laser available per protocol in all groups). These benefits were generally consistent between both ranibizumab doses tested and were replicated in the two studies. Clinically important benefits of ranibizumab versus control include the following:

Improvements in Best Corrected Visual Acuity

- Significantly more patients with substantial gains in visual acuity (≥15 letters)
- Significantly higher average gains in visual acuity
- Significantly fewer patients with substantial loss of visual acuity (≥15 letters)
- Rapid onset of beneficial effects on visual acuity (within 7 days after the first intravitreal injection)
- Sustained beneficial effects on visual acuity through both 24 (sham-controlled) and 36 months of treatment

Across a wide variety of additional visual acuity outcome measures, significant benefits of ranibizumab compared with sham were observed. Moreover, sham patients who eventually (after 2 years) crossed over to receive 1 year of monthly ranibizumab in Year 3 of RIDE and RISE did not experience the same magnitude of benefit as those randomized to ranibizumab treatment at the beginning of the studies. These results from the sham crossover suggest that 2 years of delay prior to anti-VEGF treatment for DME may result in a certain amount of potential vision being irretrievably lost.

Improvements in Retinal Anatomy

- Significant improvements in macular edema on optical coherence tomography
- Significant improvements in the extent of retinal thickening and retinal vascular leakage on color fundus photography and fluorescein angiography, respectively

Reductions in the Severity of Diabetic Retinopathy

- Substantially reduced usage of panretinal photocoagulation for proliferative (end-stage neovascular) diabetic retinopathy
- Substantial reductions in ≥2-step and ≥3-step worsening of retinopathy severity (outcomes linked to increased risk of vision loss)
- Substantial gains in ≥2-step and ≥3-step improvements in retinopathy severity
- Substantially reduced progression to proliferative diabetic retinopathy, as measured comprehensively using both anatomic findings and AE reporting

10.2 RISKS OF RANIBIZUMAB IN DME

The safety of ranibizumab in DME was investigated in the context of its well-studied safety profile in other retinal vascular diseases. In RIDE and RISE, ranibizumab treatment resulted in known anti-VEGF-related and procedure-related adverse events and was generally well-tolerated by patients with DME. As with other medical therapies, physicians need to understand the benefits and risk associated with therapeutic alternatives and individualize treatment decisions in consultation with their patients and patients' families. Through the proposed U.S. Product Label (Appendix 2), potential safety risks associated with ranibizumab in the DME population will be clearly communicated to healthcare professionals and patients. Notable safety information is reflected in Genentech's proposed revisions to the WARNINGS AND PRECAUTIONS section of the label. Additionally, currently ongoing pharmacovigilance activities, including individual case review, monthly mortality listings, literature review, and data-mining activities will continue to be conducted for ranibizumab in the DME population.

Specific Potential Ocular Risks

- Procedure-related risks (such as endophthalmitis, traumatic cataract, rhegmatogenous retinal detachment, retinal tear, increased intraocular pressure, subconjunctival hemorrhage, and eye pain).

The ocular risks of ranibizumab are, in general, common to any agent administered by intravitreal injection. Although some of these events are serious, the rates of serious procedure-related complications, such as endophthalmitis and traumatic cataract, were low in the DME studies, generally <0.05% per injection. Appropriate and aseptic injection technique can reduce the risk of these events in clinical practice. Importantly, the rate of infectious endophthalmitis in diabetic patients appeared similar to that observed in studies of ranibizumab in other retinal vascular diseases. Intravitreal ranibizumab injection also may be associated with elevations in intraocular pressure, but these are typically transient and can be managed either medically or without intervention.

These ocular risks are clearly and appropriately described in the current U.S. Product Label.

Specific Potential Systemic Risks

- Events potentially related to systemic VEGF inhibition, including thromboembolic events (such as myocardial infarction or stroke), hypertension, non-ocular hemorrhage, wound healing complications, and others; some of these events can be serious and may be fatal.

The overall percentages of patients who experienced non-ocular SAEs of special interest (serious AESIs) were similar among all groups during the 24-month sham–controlled treatment period, but were highest in the 0.5-mg ranibizumab group. A greater number of strokes and deaths from any cause were observed in the ranibizumab groups at Month 24 compared with the sham group, with more such events in the 0.5-mg group than the 0.3-mg group at Month 36; myocardial infarction was more common in the 0.3-mg group than in the 0.5-mg group. In addition, the incidence of hypertension SAEs and wound healing complications were higher in the ranibizumab groups.

Trends toward increased incidence of arteriothromboembolic events (ATEs), mainly stroke, have been observed in some prior studies of ranibizumab in neovascular AMD, and the current U.S. Product Label for ranibizumab includes a WARNING AND PRECAUTION regarding the potential risk of ATEs following intravitreal use of VEGF inhibitors.

Although causes of death were typical of patients with advanced diabetic complications, a potential relationship between these events and intravitreal use of VEGF inhibitors cannot be excluded. Genentech's proposed U.S. Product Label for ranibizumab with the DME indication adds a WARNING AND PRECAUTION regarding the increase in fatalities observed in RIDE and RISE, so that prescribing physicians can best decide the suitability of ranibizumab for the treatment of their individual patients with DME.

10.2.1 Benefit–Risk Discussion

Benefit–risk assessments are typically qualitative; different approaches to facilitate benefit–risk assessments have been recently proposed, although none have yet been universally adopted (Guo et al. 2010). Semi-quantitative or quantitative benefit–risk assessments are intended to supplement qualitative assessments, and not to replace clinical judgment. Overall, safety events should be evaluated in the context of their biological plausibility to best assess a drug's potential to cause or contribute to a particular AE.

A structured, systematic approach based on the Benefit Risk Action Team (BRAT) framework (Coplan et al. 2011; Levitan et al. 2011) was applied to produce a graphical representation of the benefit–risk profile of ranibizumab in DME. The goal is to present efficacy and safety data in a single view to facilitate benefit–risk assessment. This approach was meant to improve transparency of the assumptions used by Genentech to

evaluate the benefit–risk profile of ranibizumab in DME and relies on a set of design features as follows:

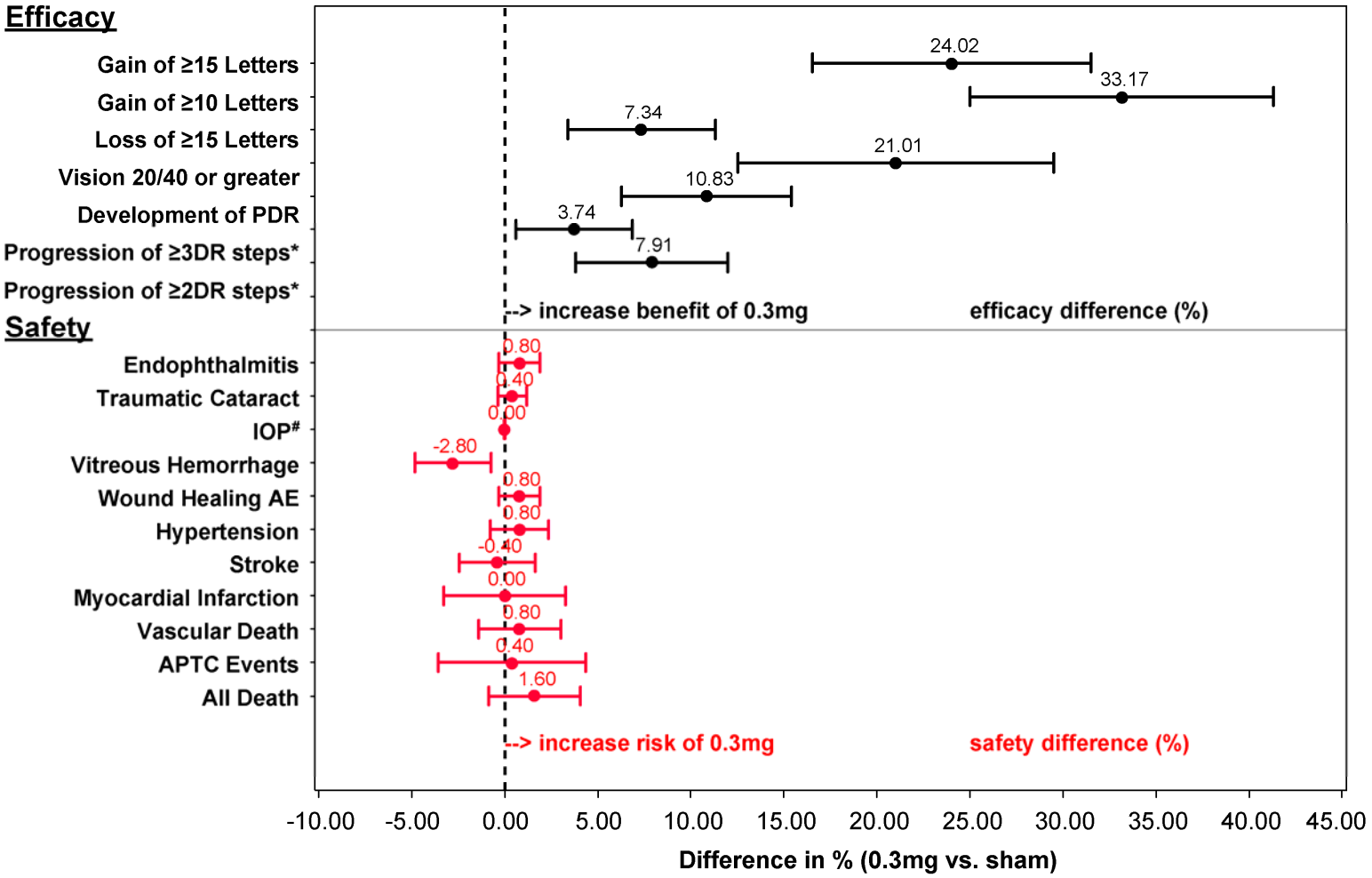
- Information from the most relevant efficacy and safety endpoints was integrated into a single graphic with little or no loss of information or distortion from the main statistical tables and listings.
- The key endpoints were ordered to allow the assessor's eye to rapidly identify the endpoints with the largest numeric contributions with regard to both benefit and risk, so that assessors can readily identify and compare the most relevant endpoints.
- The degree of uncertainty for each endpoint can be rapidly assessed by examining the confidence intervals (CIs).

Comparative benefit–risk plots were produced showing the absolute difference (and 95% CIs) between the ranibizumab and sham groups in the percentage of patients who experienced the outcome or event up to Month 24 (Figure 32 and Figure 33). For both doses of ranibizumab, clear improvements in key efficacy parameters compared with sham are shown, while differences in the rates of key AEs are relatively small in general.

At Month 24, the higher dose of 0.5-mg ranibizumab demonstrated numerically greater efficacy in some key endpoints, although the 95% confidence intervals demonstrated that the efficacy of the 0.3-mg and 0.5-mg doses was similar and that there is minimal or no true efficacy difference between the two ranibizumab dose groups (Figure 34). Conversely, at Month 24, a relatively greater numerical incidence of certain safety events occurred in the 0.5-mg group. At Month 36, the two doses appeared similar in efficacy, with no consistent incremental efficacy benefit of the 0.5-mg dose compared with the 0.3-mg dose (Figure 35). For systemic safety, the differences between the two ranibizumab doses seen at Month 24 were similar at Month 36.

In summary, for both doses of ranibizumab clear and substantial improvements in efficacy compared with sham were shown at Month 24. Moreover, the improvements seen at Month 24 with both doses of ranibizumab were maintained at Month 36. The observed differences in safety event rates among both doses of ranibizumab and sham-treated patients are generally small at Month 24, and AE rates remained stable with increased exposure to ranibizumab during the last year of the 36-month treatment period. These observations support the interpretation that the benefits of ranibizumab treatment for DME strongly outweigh the risks. Ultimately, the risks and benefits must be discussed by individual patients and physicians, and this discussion must also include consideration of short- and long-term benefits and risks of alternative treatments such as macular laser.

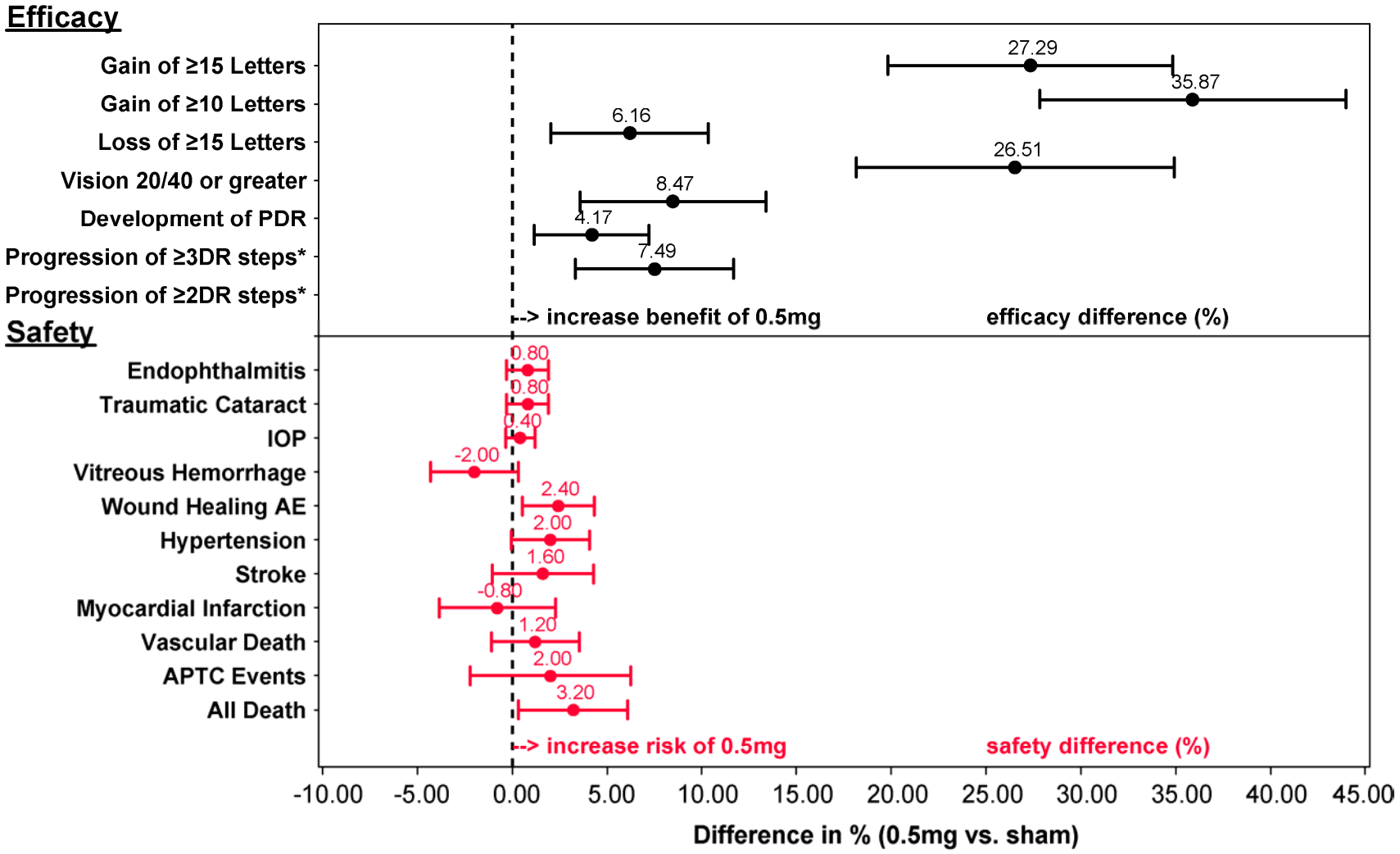
Figure 32 Benefit–Risk Plots (0.3 mg Ranibizumab vs. Sham) at Month 24: Absolute Difference (95% CI)



* On the ETDRS Diabetic Retinopathy Severity Scale.

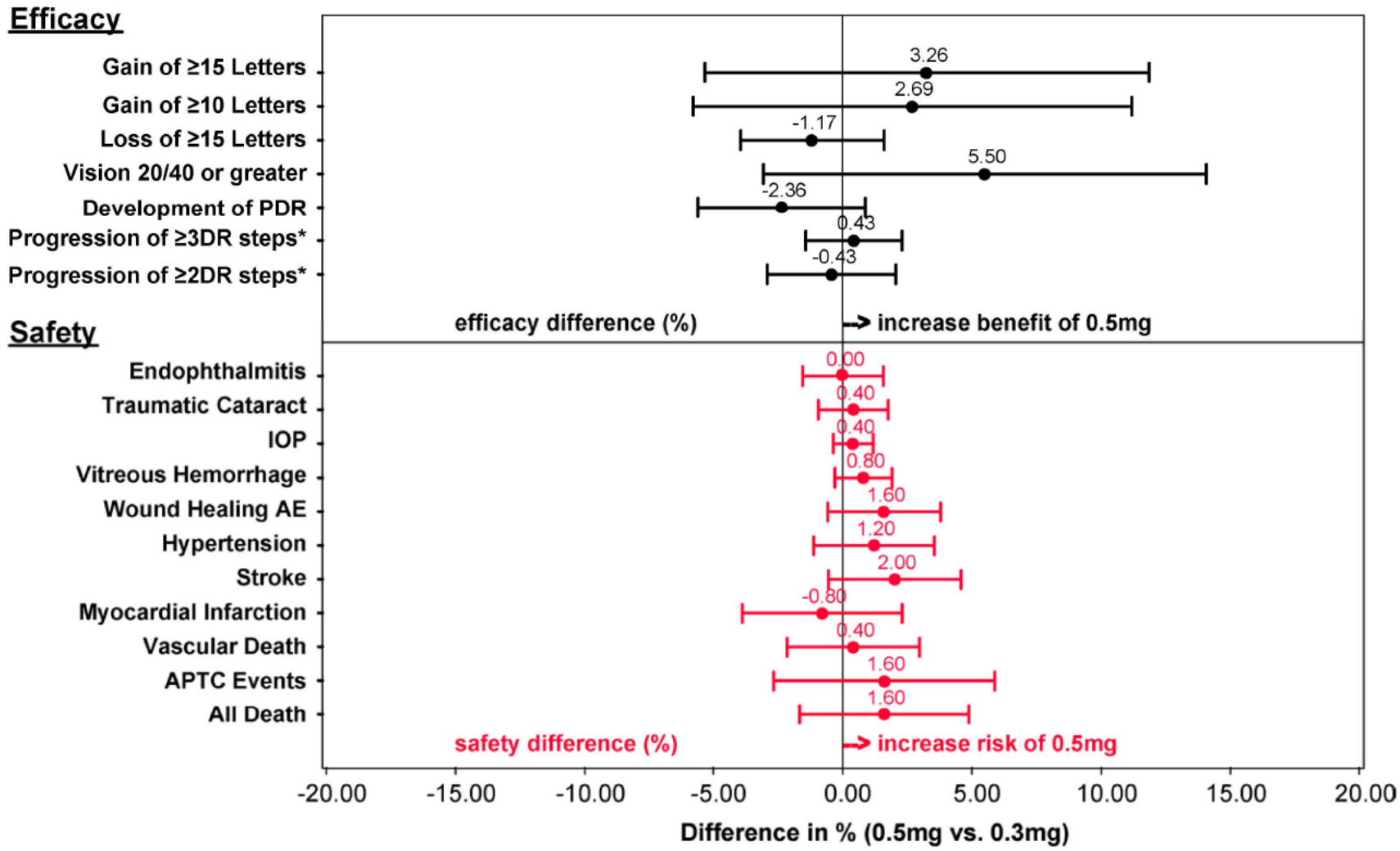
Both groups had zero events of intraocular pressure.

Figure 33 Benefit–Risk Plot (0.5 mg Ranibizumab vs. Sham) at Month 24: Absolute Difference (95% CI)



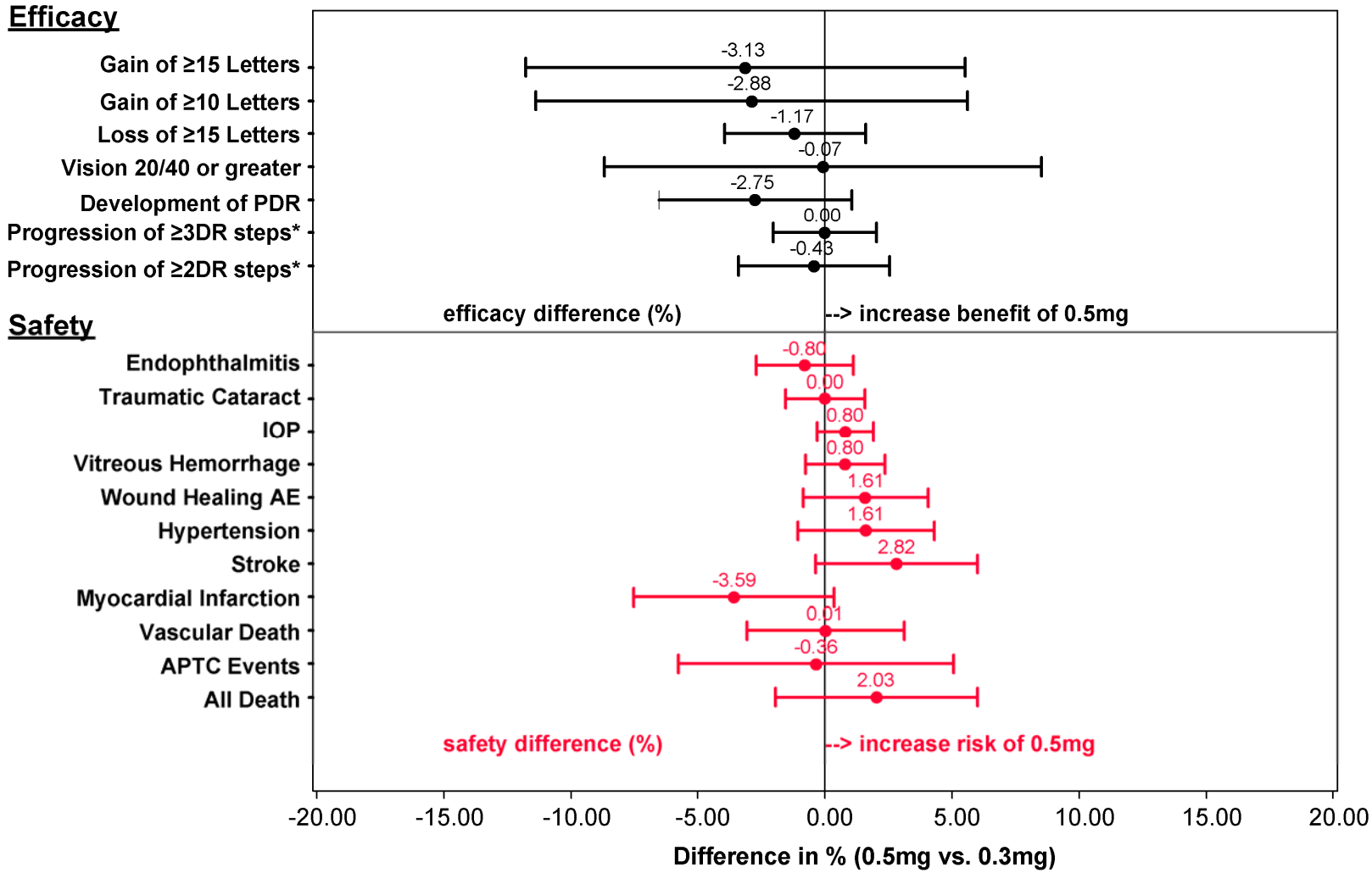
* On the ETDRS Diabetic Retinopathy Severity Scale.

Figure 34 Dose Comparison Plot (0.5 mg vs. 0.3 mg Ranibizumab) at Month 24: Absolute Difference (95% CI)



* On the ETDRS Diabetic Retinopathy Severity Scale.

Figure 35 Dose Comparison Plot (0.5 mg vs. 0.3 mg Ranibizumab) at Month 36: Absolute Difference (95% CI)



* On the ETDRS Diabetic Retinopathy Severity Scale.

10.2.2 Dose Selection

The overall dose recommendation depends on a balance of relative safety and efficacy of the tested doses, within the context of the patient population under consideration as well as the potential need for long-term therapy.

Both tested doses of ranibizumab are highly efficacious compared with sham treatment when administered monthly to patients with DME, with maintenance of effect through 36 months. The 0.3-mg and 0.5-mg doses showed similar efficacy at 24 months; the 36-month pooled outcomes of RIDE and RISE demonstrated no apparent incremental efficacy benefit of the 0.5-mg dose over the 0.3-mg dose.

From a systemic safety perspective, at 24 and 36 months, the overall incidence of APTC-classified events was similar in the 0.3-mg and 0.5-mg groups. However, overall mortality and stroke appeared to be more common in the 0.5-mg group compared with the 0.3-mg group, and overall non-ocular SAEs and adverse events of special interest occurred in higher numbers of DME patients treated with 0.5 mg than with 0.3 mg ranibizumab. Although observations of increased stroke and death relative to control were not seen in other 1–2-year studies of 0.5 mg ranibizumab in DME in which the 0.5-mg dose was administered less intensively (Elman et al. 2011; Mitchell et al. 2011), on the basis of the totality of the clinical trial safety and efficacy data in RIDE and RISE, and especially because there appear to be no incremental benefits from the higher (0.5-mg) dose, Genentech recommends the 0.3-mg dose of ranibizumab administered monthly for patients with DME.

10.3 CONCLUSIONS

The effects of ranibizumab on visual acuity and macular edema in patients with DME, as observed in RIDE and RISE and reviewed above, provide evidence that anti-VEGF therapy with ranibizumab results in substantial and clinically meaningful visual and anatomic benefits. Ranibizumab was generally well tolerated in patients with DME. The favorable outcomes in both visual acuity and macular edema seen with ranibizumab, beginning at Day 7 and sustained through 36 months, provide compelling evidence of clinical benefits. Furthermore, ranibizumab treatment offers significant benefits compared with other therapies used for DME, such as macular laser, in that it offers increased effectiveness as measured by every endpoint assessing vision, retinal anatomy, and disease severity. This benefit is weighed against a safety profile consistent with the known ranibizumab and/or anti-VEGF- and procedure-related adverse events observed in the DME clinical studies.

It is challenging to provide a simple decision algorithm on the trade-offs that patients and their caregivers are willing to accept in assessing the benefit–risk of ranibizumab for DME. Although the benefits on vision are strongly compelling, uncommon but serious adverse events cannot be excluded in association with intravitreal ranibizumab treatment. Given the value that patients place on preservation and restoration of vision

(Brown et al. 1999; Brown et al. 2001), and that blindness is a complication feared more than any other morbid complication of diabetes (Aiello 2005), the benefit–risk ratio of ranibizumab as a treatment for DME is highly favorable.

On the basis of the findings of studies RIDE and RISE, Genentech seeks FDA approval for intravitreal ranibizumab as a treatment for patients with DME.

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Appendix 1 Currently Approved Lucentis® U.S. Product Label

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use LUCENTIS safely and effectively. See full prescribing information for LUCENTIS.

LUCENTIS® (ranibizumab injection)
Intravitreal Injection
Initial U.S. Approval: 2006

----------RECENT MAJOR CHANGES----------

- Indications and Usage, Macular Edema Following Retinal Vein Occlusion (RVO) (1.2), 6/2010
- Dosage and Administration, Macular Edema Following Retinal Vein Occlusion (RVO) (2.3), 6/2010
- Warnings and Precautions, Thromboembolic Events (5.3), 6/2010

----------INDICATIONS AND USAGE----------

LUCENTIS is indicated for the treatment of patients with:

- Neovascular (Wet) Age-Related Macular Degeneration (AMD) (1.1)
- Macular Edema Following Retinal Vein Occlusion (RVO) (1.2)

----------DOSAGE AND ADMINISTRATION----------

FOR OPHTHALMIC INTRAVITREAL INJECTION ONLY (2.1)

Neovascular (Wet) Age-Related Macular Degeneration (AMD)

- LUCENTIS 0.5 mg (0.05 mL) is recommended to be administered by intravitreal injection once a month (approximately 28 days) (2.2).
- Although less effective, treatment may be reduced to one injection every three months after the first four injections if monthly injections are not feasible. Compared to continued monthly dosing, dosing every 3 months will lead to an approximate 5-letter (1-line) loss of visual acuity benefit, on average, over the following 9 months. Patients should be treated regularly (2.2).

Macular Edema Following Retinal Vein Occlusion (RVO)

- LUCENTIS 0.5 mg (0.05 mL) is recommended to be administered by intravitreal injection once a month (approximately 28 days). In the RVO clinical studies, patients received monthly injections of LUCENTIS for six months. In spite of being guided by optical coherence tomography and visual acuity re-treatment criteria, patients who were then not treated at Month 6 experienced on average, a loss of visual acuity at Month 7, whereas patients who were treated at Month 6 did not. Patients should be treated monthly (2 3).

----------DOSAGE FORMS AND STRENGTHS----------

- 10 mg/mL solution in a single-use vial for intravitreal injection (3)

----------CONTRAINDICATIONS----------

- Ocular or periocular infections (4.1)
- Hypersensitivity (4.2)

----------WARNINGS AND PRECAUTIONS----------

- Endophthalmitis and retinal detachments may occur following intravitreal injections. Patients should be monitored during the week following the injection (5.1).
- Increases in intraocular pressure have been noted within 60 minutes of intravitreal injection (5.2).

----------ADVERSE REACTIONS----------

- The most common adverse reactions (reported more frequently in LUCENTIS-treated subjects than control subjects) are conjunctival hemorrhage, eye pain, vitreous floaters, increased intraocular pressure, and intraocular inflammation (6.2).

To report SUSPECTED ADVERSE REACTIONS, contact Genentech at 1-888-835-2555 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 6/2010

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the Full Prescribing Information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE
LUCENTIS is indicated for the treatment of patients with:

1.1 Neovascular (Wet) Age-Related Macular Degeneration (AMD)

1.2 Macular Edema Following Retinal Vein Occlusion (RVO)

2 DOSAGE AND ADMINISTRATION

2.1 General Dosing Information
FOR OPHTHALMIC INTRAVITREAL INJECTION ONLY.

2.2 Neovascular (Wet) Age-Related Macular Degeneration (AMD)
LUCENTIS 0.5 mg (0.05 mL) is recommended to be administered by intravitreal injection once a month (approximately 28 days).

Although less effective, treatment may be reduced to one injection every three months after the first four injections if monthly injections are not feasible. Compared to continued monthly dosing, dosing every 3 months will lead to an approximate 5-letter (1-line) loss of visual acuity benefit, on average, over the following 9 months. Patients should be treated regularly [*see Clinical Studies (14.2)*].

2.3 Macular Edema Following Retinal Vein Occlusion (RVO)
LUCENTIS 0.5 mg (0.05 mL) is recommended to be administered by intravitreal injection once a month (approximately 28 days).

In Studies RVO-1 and RVO-2, patients received monthly injections of LUCENTIS for six months. In spite of being guided by optical coherence tomography and visual acuity re-treatment criteria, patients who were then not treated at Month 6 experienced on average, a loss of visual acuity at Month 7, whereas patients who were treated at Month 6 did not. Patients should be treated monthly [*see Clinical Studies (14.2)*].

2.4 Preparation for Administration
Using aseptic technique, all (0.2 mL) of the LUCENTIS vial contents are withdrawn through a 5-micron, 19-gauge filter needle attached to a 1-cc tuberculin syringe. The filter needle should be discarded after withdrawal of the vial contents and should not be used for intravitreal injection. The filter needle should be replaced with a sterile 30-gauge × 1/2-inch needle for the intravitreal injection. The contents should be expelled until the plunger tip is aligned with the line that marks 0.05 mL on the syringe.

2.5 Administration
The intravitreal injection procedure should be carried out under controlled aseptic conditions, which include the use of sterile gloves, a sterile drape, and a sterile eyelid speculum (or equivalent). Adequate anesthesia and a broad-spectrum microbicide should be given prior to the injection.

Following the intravitreal injection, patients should be monitored for elevation in intraocular pressure and for endophthalmitis. Monitoring may consist of a check for perfusion of the optic nerve head immediately after the injection and tonometry within 30 minutes following the injection. Patients should be instructed to report any symptoms suggestive of endophthalmitis without delay.

Each vial should only be used for the treatment of a single eye. If the contralateral eye requires treatment, a new vial should be used and the sterile field, syringe, gloves, drapes, eyelid speculum, filter, and injection needles should be changed before LUCENTIS is administered to the other eye.

No special dosage modification is required for any of the populations that have been studied (e.g., gender, elderly).

3 DOSAGE FORMS AND STRENGTHS
Single-use glass vial designed to provide 0.05 mL of 10 mg/mL solution for intravitreal injection.

4 CONTRAINDICATIONS

4.1 Ocular or Periocular Infections
LUCENTIS is contraindicated in patients with ocular or periocular infections.

4.2 Hypersensitivity
LUCENTIS is contraindicated in patients with known hypersensitivity to ranibizumab or any of the excipients in LUCENTIS. Hypersensitivity reactions may manifest as severe intraocular inflammation.

5 WARNINGS AND PRECAUTIONS

5.1 Endophthalmitis and Retinal Detachments
Intravitreal injections, including those with LUCENTIS, have been associated with endophthalmitis and retinal detachments. Proper aseptic injection technique should always be used when administering LUCENTIS. In addition, patients should be monitored during the week following the injection to permit early treatment should an infection occur [*see Dosage and Administration (2.4, 2.5) and Patient Counseling Information (17)*].

5.2 Increases in Intraocular Pressure
Increases in intraocular pressure have been noted within 60 minutes of intravitreal injection with LUCENTIS. Therefore, intraocular pressure as well as the perfusion of the optic nerve head should be monitored and managed appropriately [*see Dosage and Administration (2.5)*].

5.3 Thromboembolic Events
Although there was a low rate of arterial thromboembolic events (ATEs) observed in the LUCENTIS clinical trials, there is a potential risk of ATEs following intravitreal use of VEGF inhibitors. ATEs are defined as nonfatal stroke, nonfatal myocardial infarction, or vascular death (including deaths of unknown cause).

Neovascular (Wet) Age-Related Macular Degeneration
The ATE rate in the three controlled neovascular AMD studies during the first year was 1.9% (17 out of 874) in the combined group of patients treated with 0.3 mg or 0.5 mg LUCENTIS compared with 1.1% (5 out of 441) in patients from the control arms [see Clinical Studies (14.1)]. In the second year of studies AMD-1 and AMD-2, the ATE rate was 2.6% (19 out of 721) in the combined group of LUCENTIS-treated patients compared with 2 9% (10 out of 344) in patients from the control arms.

In a pooled analysis of 2-year controlled studies (AMD-1, AMD-2 and a study of LUCENTIS used adjunctively with verteporfin photodynamic therapy), the stroke rate (including both ischemic and hemorrhagic stroke) was 2.7% (13 out of 484) in patients treated with 0.5 mg LUCENTIS compared to 1 1% (5 out of 435) in patients in the control arms (odds ratio 2.2 (95% confidence interval (0.8-7.1))).

Macular Edema Following Retinal Vein Occlusion
The ATE rate in the two controlled RVO studies during the first six months was 0.8% in both the LUCENTIS and control arms of the studies (4 out of 525 in the combined group of patients treated with 0.3 mg or 0.5 mg LUCENTIS and 2 out of 260 in the control arms) [*see Clinical Studies (14.2)*]. The stroke rate was 0.2% (1 out of 525) in the combined group of LUCENTIS-treated patients compared to 0.4% (1 out of 260) in the control arms.

6 ADVERSE REACTIONS
Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in one clinical trial of a drug cannot be directly compared with rates in the clinical trials of the same or another drug and may not reflect the rates observed in practice.

6.1 Injection Procedure
Serious adverse reactions related to the injection procedure have occurred in <0.1% of intravitreal injections, including endophthalmitis [*see Warnings and Precautions (5.1)*], rhegmatogenous retinal detachments, and iatrogenic traumatic cataracts.

6.2 Clinical Studies Experience
The data below reflect exposure to 0.5 mg LUCENTIS in 440 patients with neovascular AMD in three double-masked, controlled studies (AMD-1, AMD-2, and AMD-3) [*see Clinical Studies (14.1)*] as well as exposure to 0.5 mg LUCENTIS in 259 patients with macular edema following RVO in two double-masked, controlled studies (RVO-1 and RVO-2) [*see Clinical Studies (14.2)*].

Ocular Reactions
Table 1 shows frequently reported ocular adverse reactions in LUCENTIS treated patients compared with the control group.

Table 1
Ocular Reactions in AMD and RVO Studies

Adverse Reaction	AMD 2-year		AMD 1-year		RVO 6-month	
	LUCENTIS n=379	Control n=379	LUCENTIS n=440	Control n=441	LUCENTIS n=259	Control n=260
Conjunctival hemorrhage	74%	60%	64%	50%	48%	37%
Eye pain	35%	30%	26%	20%	17%	12%
Vitreous floaters	27%	8%	19%	5%	7%	2%
Intraocular pressure increased	24%	7%	17%	5%	7%	2%
Vitreous detachment	21%	19%	15%	15%	4%	2%
Intraocular inflammation	18%	8%	13%	7%	1%	3%
Cataract	17%	14%	11%	9%	2%	2%
Foreign body sensation in eyes	16%	14%	13%	10%	7%	5%
Eye irritation	15%	15%	13%	12%	7%	6%
Lacrimation increased	14%	12%	8%	8%	2%	3%
Blepharitis	12%	8%	8%	5%	0%	1%
Dry eye	12%	7%	7%	7	3%	3%
Visual disturbance or vision blurred	18%	15%	13%	10%	5%	3%
Eye pruritis	12%	11%	9%	7%	1%	2%
Ocular hyperemia	11%	8%	7%	4%	5%	3%
Retinal disorder	10%	7%	8%	4%	2%	1%
Maculopathy	9%	9%	6%	6%	11%	7%
Retinal degeneration	8%	6%	5%	3%	1%	0%
Ocular discomfort	7%	4%	5%	2%	2%	2%
Conjunctival hyperemia	7%	6%	5%	4%	0%	0%
Posterior capsule opacification	7%	4%	2%	2%	0%	1%
Injection site hemorrhage	5%	2%	3%	1%	0%	0%

Non-Ocular Reactions
Table 2 shows frequently reported non-ocular adverse reactions in LUCENTIS treated patients compared with the control group.

Table 2
Non-Ocular Reactions in AMD and RVO Studies

Adverse Reaction	AMD 2-year		AMD 1-year		RVO 6-month	
	LUCENTIS n=379	Control n=379	LUCENTIS n=440	Control n=441	LUCENTIS n=259	Control n=260
Nasopharyngitis	16%	13%	8%	9%	5%	4%
Headache	12%	9%	6%	5%	3%	3%
Arthralgia	11%	9%	5%	5%	2%	1%
Bronchitis	11%	9%	6%	5%	0%	2%
Urinary tract infection	9%	9%	5%	5%	1%	2%
Cough	9%	8%	5%	4%	2%	2%
Nausea	9%	6%	5%	5%	1%	2%
Upper respiratory tract infection	9%	8%	5%	5%	2%	2%
Sinusitis	8%	7%	5%	5%	3%	2%
Anemia	8%	7%	4%	3%	1%	1%
Influenza	7%	5%	3%	2%	3%	2%
Chronic obstructive pulmonary disease	6%	3%	1%	0%	0%	0%
Hypercholesterolemia	5%	5%	3%	2%	1%	1%
Insomnia	5%	5%	3%	2%	1%	1%
Pain in extremity	5%	6%	3%	2%	1%	1%
Atrial fibrillation	5%	4%	2%	2%	1%	0%
Anxiety	4%	4%	3%	2%	1%	2%
Dyspnea	4%	3%	2%	2%	0%	0%
Gastroenteritis viral	4%	1%	3%	1%	1%	0%

6.3 Immunogenicity

As with all therapeutic proteins, there is the potential for an immune response in patients treated with LUCENTIS. The immunogenicity data reflect the percentage of patients whose test results were considered positive for antibodies to LUCENTIS in immunoassays and are highly dependent on the sensitivity and specificity of the assays.

The pre-treatment incidence of immunoreactivity to LUCENTIS was 0%–5% across treatment groups. After monthly dosing with LUCENTIS for 6 to 24 months, antibodies to LUCENTIS were detected in approximately 1%-8% of patients.

The clinical significance of immunoreactivity to LUCENTIS is unclear at this time. Among neovascular AMD patients with the highest levels of immunoreactivity, some were noted to have iritis or vitritis. Intraocular inflammation was not observed in the RVO patients with the highest levels of immunoreactivity.

7 DRUG INTERACTIONS

Drug interaction studies have not been conducted with LUCENTIS.

LUCENTIS intravitreal injection has been used adjunctively with verteporfin photodynamic therapy (PDT). Twelve of 105 (11%) patients with neovascular AMD developed serious intraocular inflammation; in 10 of the 12 patients, this occurred when LUCENTIS was administered 7 days (±2 days) after verteporfin PDT.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy
Pregnancy Category C. Animal reproduction studies have not been conducted with ranibizumab. It is also not known whether ranibizumab can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. LUCENTIS should be given to a pregnant woman only if clearly needed.

8.3 Nursing Mothers
It is not known whether ranibizumab is excreted in human milk. Because many drugs are excreted in human milk, and because the potential for absorption and harm to infant growth and development exists, caution should be exercised when LUCENTIS is administered to a nursing woman.

8.4 Pediatric Use
The safety and effectiveness of LUCENTIS in pediatric patients has not been established.

8.5 Geriatric Use
In the clinical studies, approximately 82% (1146/1406) of the patients randomized to treatment with LUCENTIS were ≥ 65 years of age and approximately 55% (772/1406) were ≥ 75 years of age. No notable differences in efficacy or safety were seen with increasing age in these studies. Age did not have a significant effect on systemic exposure in population pharmacokinetic analyses after correcting for creatinine clearance.

8.6 Patients with Renal Impairment
No formal studies have been conducted to examine the pharmacokinetics of ranibizumab in patients with renal impairment. In population pharmacokinetic analyses of patients, 54% (389/725) had renal impairment (39% mild, 12% moderate, and 2% severe). The reduction in ranibizumab clearance in patients with renal impairment is considered clinically insignificant. Dose adjustment is not expected to be needed for patients with renal impairment.

8.7 Patients with Hepatic Dysfunction
No formal studies have been conducted to examine the pharmacokinetics of ranibizumab in patients with hepatic impairment. Dose adjustment is not expected to be needed for patients with hepatic dysfunction.

10 OVERDOSAGE
Planned initial single doses of ranibizumab injection 1 mg were associated with clinically significant intraocular inflammation in 2 of 2 neovascular AMD patients injected. With an escalating regimen of doses beginning with initial doses of ranibizumab injection 0.3 mg, doses as high as 2 mg were tolerated in 15 of 20 neovascular AMD patients.

11 DESCRIPTION
LUCENTIS® (ranibizumab injection) is a recombinant humanized IgG1 kappa isotype monoclonal antibody fragment designed for intraocular use. Ranibizumab binds to and inhibits the biologic activity of human vascular endothelial growth factor A (VEGF-A). Ranibizumab has a molecular weight of approximately 48 kilodaltons and is produced by an *E. coli* expression system in a nutrient medium containing the antibiotic tetracycline. Tetracycline is not detectable in the final product.

LUCENTIS is a sterile, colorless to pale yellow solution in a single-use glass vial. LUCENTIS is supplied as a preservative-free, sterile solution in a single-use glass vial designed to deliver 0.05 mL of 10 mg/mL LUCENTIS aqueous solution with 10 mM histidine HCl, 10% α,α-trehalose dihydrate, 0.01% polysorbate 20, pH 5.5.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action
Ranibizumab binds to the receptor binding site of active forms of VEGF-A, including the biologically active, cleaved form of this molecule, $VEGF_{110}$. VEGF-A has been shown to cause neovascularization and leakage in models of ocular angiogenesis and vascular occlusion, and is thought to contribute to the progression of neovascular AMD and macular edema following RVO. The binding of ranibizumab to VEGF-A prevents the interaction of VEGF-A with its receptors (VEGFR1 and VEGFR2) on the surface of endothelial cells, reducing endothelial cell proliferation, vascular leakage, and new blood vessel formation.

12.2 Pharmacodynamics
Increased center point thickness (CPT) as assessed by optical coherence tomography (OCT) is associated with neovascular AMD and macular edema following RVO. Leakage from choroidal neovascularization (CNV) as assessed by fluorescein angiography is associated with neovascular AMD.

Neovascular (Wet) Age-Related Macular Degeneration
In Study AMD-3, CPT was assessed by OCT in 118/184 patients. OCT measurements were collected at baseline, Months 1, 2, 3, 5, 8, and 12. In patients treated with LUCENTIS, CPT decreased, on average, more than the sham group from baseline through Month 12. CPT decreased by Month 1 and decreased further at Month 3, on average. CPT data did not provide information useful in influencing treatment decisions [*see Clinical Studies (14.1)*].

In patients treated with LUCENTIS, the area of vascular leakage, on average, decreased by Month 3 as assessed by fluorescein angiography. The area of vascular leakage for an individual patient was not correlated with visual acuity.

Macular Edema Following Retinal Vein Occlusion
On average, CPT reductions were observed in Studies RVO-1 and RVO-2 beginning at Day 7 following the first LUCENTIS injection through Month 6. CPT was not evaluated as a means to guide treatment decisions [*see Clinical Studies (14.2)*].

12.3 Pharmacokinetics
In animal studies, following intravitreal injection, ranibizumab was cleared from the vitreous with a half-life of approximately 3 days. After reaching a maximum at approximately 1 day, the serum concentration of ranibizumab declined in parallel with the vitreous concentration. In these animal studies, systemic exposure of ranibizumab is more than 2000-fold lower than in the vitreous.

In patients with neovascular AMD, following monthly intravitreal administration, maximum ranibizumab serum concentrations were low (0 3 ng/mL to 2.36 ng/mL). These levels were below the concentration of ranibizumab (11 ng/mL to 27 ng/mL) thought to be necessary to inhibit the biological activity of VEGF-A by 50%, as measured in an in vitro cellular proliferation assay. The maximum observed serum concentration was dose proportional over the dose range of 0.05 to 1 mg/eye. Serum ranibizumab concentrations in RVO patients were similar to those observed in neovascular AMD patients.

Based on a neovascular AMD population pharmacokinetic analysis, maximum serum concentrations of 1.5 ng/mL are predicted to be reached at approximately 1 day after monthly intravitreal administration of LUCENTIS 0.5 mg/eye. Based on the disappearance of ranibizumab from serum, the estimated average vitreous elimination half-life was approximately 9 days. Steady-state minimum concentration is predicted to be 0.22 ng/mL with a monthly dosing regimen. In humans, serum ranibizumab concentrations are predicted to be approximately 90,000-fold lower than vitreal concentrations.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
No carcinogenicity or mutagenicity data are available for ranibizumab injection in animals or humans.

No studies on the effects of ranibizumab on fertility have been conducted.

14 CLINICAL STUDIES

14.1 *Neovascular (Wet) Age-Related Macular Degeneration (AMD)*
The safety and efficacy of LUCENTIS were assessed in three randomized, double-masked, sham- or active-controlled studies in patients with neovascular AMD. A total of 1323 patients (LUCENTIS 879, Control 444) were enrolled in the three studies.

Studies AMD-1 and AMD-2
In Study AMD-1, patients with minimally classic or occult (without classic) CNV lesions received monthly LUCENTIS 0.3 mg or 0 5 mg intravitreal injections or monthly sham injections. Data are available through Month 24. Patients treated with LUCENTIS in Study AMD-1 received a mean of 22 total treatments out of a possible 24 from Day 0 to Month 24.

In Study AMD-2, patients with predominantly classic CNV lesions received one of the following: 1) monthly LUCENTIS 0.3 mg intravitreal injections and sham PDT; 2) monthly LUCENTIS 0.5 mg intravitreal injections and sham PDT; or 3) sham intravitreal injections and active verteporfin PDT. Sham PDT (or active verteporfin PDT) was given with the initial LUCENTIS (or sham) intravitreal injection and every 3 months thereafter if fluorescein angiography showed persistence or recurrence of leakage. Data are available through Month 24. Patients treated with LUCENTIS in Study AMD-2 received a mean of 21 total treatments out of a possible 24 from Day 0 through Month 24.

In both studies, the primary efficacy endpoint was the proportion of patients who maintained vision, defined as losing fewer than 15 letters of visual acuity at 12 months compared with baseline. Almost all LUCENTIS-treated patients (approximately 95%) maintained their visual acuity. 34%–40% of LUCENTIS-treated patients experienced a clinically significant improvement in vision, defined as gaining 15 or more letters at 12 months. The size of the lesion did not significantly affect the results. Detailed results are shown in the Table 3, Table 4, and Figure 1 below.

Table 3

Outcomes at Month 12 and Month 24 in Study AMD-1

Outcome Measure	Month	Sham n = 238	LUCENTIS 0.5 mg n = 240	Estimated Difference (95% CI)[a]
Loss of < 15 letters in visual acuity (%)[b]	12	62%	95%	32% (26%, 39%)
	24	53%	90%	37% (29%, 44%)
Gain of ≥ 15 letters in visual acuity (%)[b]	12	5%	34%	29% (22%, 35%)
	24	4%	33%	29% (23%, 35%)
Mean change in visual acuity (letters) (SD)[b]	12	−10.5 (16.6)	+7.2 (14.4)	17 5 (14.8, 20.2)
	24	−14.9 (18.7)	+6.6 (16.5)	21.1 (18.1, 24.2)

[a] Adjusted estimate based on the stratified model.
[b] $p < 0.01$.

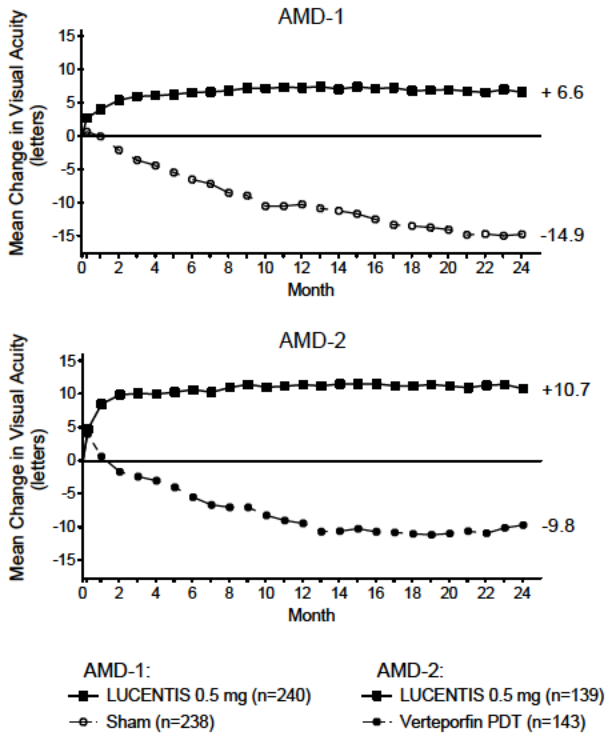
Table 4

Outcomes at Month 12 and Month 24 in Study AMD-2

Outcome Measure	Month	Verteporfin PDT n = 143	LUCENTIS 0 5 mg n = 139	Estimated Difference (95% CI)[a]
Loss of < 15 letters in visual acuity (%)[b]	12	64%	96%	33% (25%, 41%)
	24	66%	90%	25% (16%, 34%)
Gain of ≥ 15 letters in visual acuity (%)[b]	12	6%	40%	35% (26%, 44%)
	24	6%	41%	35% (26%, 44%)
Mean change in visual acuity (letters) (SD)[b]	12	−9.5 (16.4)	+11.3 (14.6)	21.1 (17.5, 24.6)
	24	−9.8 (17.6)	+10.7 (16.5)	20.7 (16.8, 24.7)

[a] Adjusted estimate based on the stratified model.
[b] $p < 0.01$.

Figure 1
Mean Change in Visual Acuity from Baseline to Month 24 in Study AMD-1 and Study AMD-2

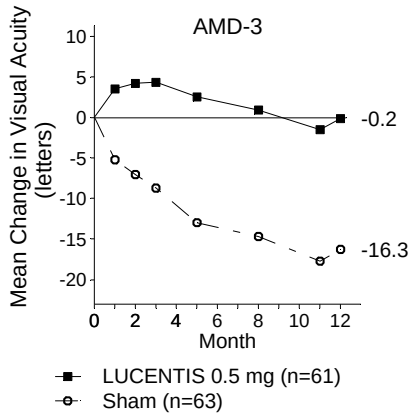


Patients in the group treated with LUCENTIS had minimal observable CNV lesion growth, on average. At Month 12, the mean change in the total area of the CNV lesion was 0.1–0.3 DA for LUCENTIS versus 2 3–2.6 DA for the control arms. At Month 24, the mean change in the total area of the CNV lesion was 0.3–0.4 DA for LUCENTIS versus 2.9–3.1 DA for the control arms.

Study AMD-3
Study AMD-3 was a randomized, double-masked, sham-controlled, two-year study designed to assess the safety and efficacy of LUCENTIS in patients with neovascular AMD (with or without a classic CNV component). Data are available through Month 12. Patients received LUCENTIS 0.3 mg or 0.5 mg intravitreal injections or sham injections once a month for 3 consecutive doses, followed by a dose administered once every 3 months for 9 months. A total of 184 patients were enrolled in this study (LUCENTIS 0.3 mg, 60; LUCENTIS 0.5 mg, 61; sham, 63); 171 (93%) completed 12 months of this study. Patients treated with LUCENTIS in Study AMD-3 received a mean of 6 total treatments out of a possible 6 from Day 0 through Month 12.

In Study AMD-3, the primary efficacy endpoint was mean change in visual acuity at 12 months compared with baseline (see Figure 2). After an initial increase in visual acuity (following monthly dosing), on average, patients dosed once every three months with LUCENTIS lost visual acuity, returning to baseline at Month 12. In Study AMD-3, almost all LUCENTIS-treated patients (90%) maintained their visual acuity at Month 12.

Figure 2
Mean Change in Visual Acuity from Baseline to Month 12 in Study AMD-3



14.2 Macular Edema Following Retinal Vein Occlusion (RVO)
The safety and efficacy of LUCENTIS were assessed in two randomized, double-masked, one-year studies in patients with macular edema following RVO. Sham controlled data are available through Month 6. Patient age ranged from 20 to 91 years, with a mean age of 67 years. A total of 789 patients (LUCENTIS 0.3 mg, 266 patients; LUCENTIS 0.5 mg, 261 patients; sham, 262 patients) were enrolled, with 739 (94%) patients completing through Month 6. All patients completing Month 6 were eligible to receive LUCENTIS injections guided by pre-specified re-treatment criteria until the end of the studies at Month 12.

In Study RVO-1, patients with macular edema following branch or hemi-RVO, received monthly LUCENTIS 0.3 mg or 0 5 mg intravitreal injections or monthly sham injections for 6 months. All patients were eligible for rescue laser treatment beginning at Month 3 of the 6 month treatment period. Rescue laser treatment was given to 26 of 131 (20%) patients treated with 0.5 mg LUCENTIS and 72 of 132 (55%) patients treated with sham.

In Study RVO-2, patients with macular edema following central RVO received monthly LUCENTIS 0.3 mg or 0 5 mg intravitreal injections or monthly sham injections for 6 months.

At Month 6, after monthly treatment with 0.5 mg LUCENTIS, the following clinical results were observed:

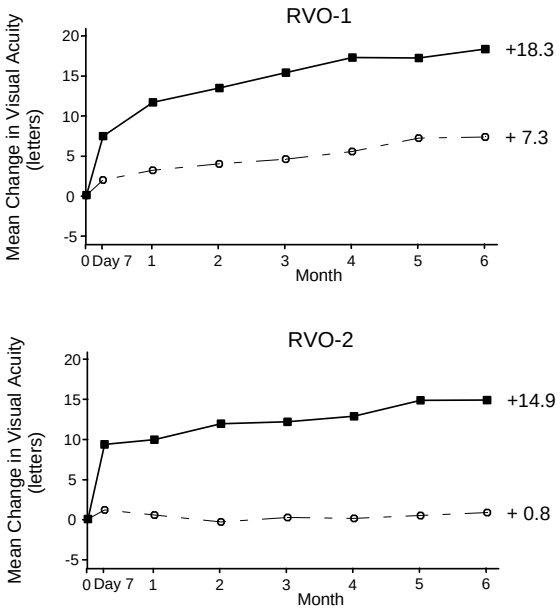
Table 5

Percentage of Patients with Gain of ≥15 letters in Visual Acuity from Baseline to Month 6 in Study RVO-1 and Study RVO-2

Study	Sham	LUCENTIS 0 5 mg	Estimated Difference (95% CI)
RVO-1	29%	61%	31%[a] (20%, 43%)
RVO-2	17%	48%	30%[a] (20%, 41%)

[a] $p < 0.01$, adjusted estimate based on stratified model

Figure 3
Mean Change in Visual Acuity from Baseline to Month 6 in Study RVO-1 and Study RVO-2



$p < 0.01$ for all time points

16 HOW SUPPLIED/STORAGE AND HANDLING
Each LUCENTIS carton, NDC 50242-080-01, contains a 0.2 mL fill of 10 mg/mL ranibizumab in a 2-cc glass vial; one 5-micron, 19-gauge × 1-1/2-inch filter needle for withdrawal of the vial contents; one 30-gauge × 1/2-inch injection needle for the intravitreal injection; and one package insert [*see Dosage and Administration (2.5)*]. VIALS ARE FOR SINGLE EYE USE ONLY.

LUCENTIS should be refrigerated at 2 –8 C (36 –46 F). DO NOT FREEZE. Do not use beyond the date stamped on the label. LUCENTIS vials should be protected from light. Store in the original carton until time of use.

17 PATIENT COUNSELING INFORMATION
In the days following LUCENTIS administration, patients are at risk of developing endophthalmitis. If the eye becomes red, sensitive to light, painful, or develops a change in vision, the patient should seek immediate care from an ophthalmologist [*see Warnings and Precautions (5.1)*].

LUCENTIS® [ranibizumab injection]
Manufactured by:
Genentech, Inc.
A Member of the Roche Group
1 DNA Way
South San Francisco, CA 94080-4990

4851401
Initial US Approval June 2006
Revision Date June 2010
LUCENTIS® is a registered trademark of Genentech, Inc.

Appendix 2 Proposed Lucentis® U.S. Product Label

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use LUCENTIS safely and effectively. See full prescribing information for LUCENTIS.

LUCENTIS® (ranibizumab injection)
Intravitreal Injection
Initial U.S. Approval: 2006

----------RECENT MAJOR CHANGES----------

- Indications and Usage, Diabetic Macular Edema (DME) (1 3) xx/201x
- Dosage and Administration, DME (2 4) xx/201x
- Warnings and Precautions, Thromboembolic Events (5 3) xx/201x
- Warnings and Precautions, Fatal Events in DME Patients (5 4) xx/201x
- ~~Indications and Usage, Macular Edema Following Retinal Vein Occlusion (RVO) (1 2), 6/2010~~
- ~~Dosage and Administration, Macular Edema Following Retinal Vein Occlusion (RVO) (2 3), 6/2010~~
- ~~Warnings and Precautions, Thromboembolic Events (5 3), 6/2010~~

----------INDICATIONS AND USAGE----------

LUCENTIS is indicated for the treatment of patients with:

- Neovascular (Wet) Age-Related Macular Degeneration (AMD) (1 1)
- Macular Edema Following Retinal Vein Occlusion (RVO) (1 2)
- Diabetic Macular Edema (DME) (1 3)

----------DOSAGE AND ADMINISTRATION----------

FOR OPHTHALMIC INTRAVITREAL INJECTION ONLY (2 1)

Neovascular (Wet) Age-Related Macular Degeneration (AMD) (2.2)

- LUCENTIS 0 5 mg (0 05 mL) is recommended to be administered by intravitreal injection once a month (approximately 28 days) ~~(2 2)~~
- Although less effective, treatment may be reduced to one injection every three months after the first four injections if monthly injections are not feasible ~~Compared to continued monthly dosing, dosing every 3 months will lead to an approximate 5 letter (1 line) loss of visual acuity benefit, on average, over the following 9 months~~ Patients should be treated regularly ~~(2 2)~~

Macular Edema Following Retinal Vein Occlusion (RVO) (2.3)

- LUCENTIS 0 5 mg (0 05 mL) ~~is recommended to~~should be administered by intravitreal injection once a month (approximately 28 days) ~~In the RVO clinical studies, patients received monthly injections of LUCENTIS for six months In spite of being guided by optical coherence tomography and visual acuity re-treatment criteria, patients who were then not treated at Month 6 experienced on average, a loss of visual acuity at Month 7, whereas patients who were treated at Month 6 did not Patients should be treated monthly (2 3)~~

Diabetic Macular Edema (DME) (2.4)

- LUCENTIS 0 3 mg (0 05 mL) is recommended to be administered by intravitreal injection once a month (approximately 28 days)

----------DOSAGE FORMS AND STRENGTHS----------

~~**10 mg/mL solution in a single-use vial for intravitreal injection (3)**~~

Single-use glass vial designed to provide 0 05 mL for intravitreal injection:

- 10 mg/mL solution (LUCENTIS 0 5 mg) (3)
- 6 mg/mL solution (LUCENTIS 0 3 mg) (3)

----------CONTRAINDICATIONS----------

- Ocular or periocular infections (4 1)
- Hypersensitivity (4 2)

----------WARNINGS AND PRECAUTIONS----------

- Endophthalmitis and retinal detachments may occur following intravitreal injections Patients should be monitored during the week following the injection (5 1)
- Increases in intraocular pressure (IOP) have been noted within 60 minutes of intravitreal injection (5 2)
- There is a potential risk of arterial thromboembolic events following intravitreal use of VEGF inhibitors (5 3)
- Fatal events occurred more frequently in DME patients treated monthly with LUCENTIS compared with those in the control arms of the studies Although causes of death were those typical of patients with advanced diabetic complications, a potential relationship between these events and intravitreal use of VEGF inhibitors cannot be excluded (5 4)

----------ADVERSE REACTIONS----------

- The most common adverse reactions (reported more frequently in LUCENTIS-treated subjects than control subjects) are conjunctival hemorrhage, eye pain, vitreous floaters~~,~~ and increased ~~intraocular pressure, and intraocular inflammation~~ IOP (6 2)

To report SUSPECTED ADVERSE REACTIONS, contact Genentech at 1-888-835-2555 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION.

Revised: ~~6/2010~~xx/201x

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the Full Prescribing Information are not listed

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

LUCENTIS is indicated for the treatment of patients with:

1.1 Neovascular (Wet) Age-Related Macular Degeneration (AMD)

1.2 Macular Edema Following Retinal Vein Occlusion (RVO)

1.3 Diabetic Macular Edema (DME)

2 DOSAGE AND ADMINISTRATION

2.1 General Dosing Information

FOR OPHTHALMIC INTRAVITREAL INJECTION ONLY.

2.2 Neovascular (Wet) Age-Related Macular Degeneration (AMD)

LUCENTIS 0.5 mg (0.05 mL of 10 mg/mL LUCENTIS solution) is recommended to be administered by intravitreal injection once a month (approximately 28 days).

Although less effective, treatment may be reduced to one injection every three months after the first four injections if monthly injections are not feasible. Compared to continued monthly dosing, dosing every 3 months will lead to an approximate 5-letter (1-line) loss of visual acuity benefit, on average, over the following 9 months. Patients should be treated regularly [*see Clinical Studies (14.1~~2~~)*].

2.3 Macular Edema Following Retinal Vein Occlusion (RVO)

LUCENTIS 0.5 mg (0.05 mL of 10 mg/mL LUCENTIS solution) is recommended to be administered by intravitreal injection once a month (approximately 28 days).

In Studies RVO-1 and RVO-2, patients received monthly injections of LUCENTIS for six months. In spite of being guided by optical coherence tomography and visual acuity re-treatment criteria, patients who were then not treated at Month 6 experienced on average, a loss of visual acuity at Month 7, whereas patients who were treated at Month 6 did not. Patients should be treated monthly [*see Clinical Studies (14.2)*].

2.4 Diabetic Macular Edema (DME)

LUCENTIS 0.3 mg (0.05 mL of 6 mg/mL LUCENTIS solution) is recommended to be administered by intravitreal injection once a month (approximately 28 days).

2.5~~4~~ Preparation for Administration

Using aseptic technique, all (0.2 mL) of the LUCENTIS vial contents are withdrawn through a 5-micron, 19-gauge filter needle attached to a 1-cc tuberculin syringe. The filter needle should be discarded after withdrawal of the vial contents and should not be used for intravitreal injection. The filter needle should be replaced with a sterile 30-gauge×1/2-inch needle for the intravitreal injection. The contents should be expelled until the plunger tip is aligned with the line that marks 0.05 mL on the syringe.

2.65 Administration

The intravitreal injection procedure should be carried out under controlled aseptic conditions, which include the use of sterile gloves, a sterile drape, and a sterile eyelid speculum (or equivalent). Adequate anesthesia and a broad-spectrum microbicide should be given prior to the injection.

Following the intravitreal injection, patients should be monitored for elevation in intraocular pressure and for endophthalmitis. Monitoring may consist of a check for perfusion of the optic nerve head immediately after the injection and tonometry within 30 minutes following the injection. Patients should be instructed to report any symptoms suggestive of endophthalmitis without delay.

Each vial should only be used for the treatment of a single eye. If the contralateral eye requires treatment, a new vial should be used and the sterile field, syringe, gloves, drapes, eyelid speculum, filter, and injection needles should be changed before LUCENTIS is administered to the other eye.

No special dosage modification is required for any of the populations that have been studied (e.g., gender, elderly).

3 DOSAGE FORMS AND STRENGTHS

Single-use glass vial designed to provide 0.05 mL ~~of 10 mg/mL solution~~ for intravitreal injection:~~.~~

- 10 mg/mL solution (LUCENTIS 0.5 mg)
- 6 mg/mL solution (LUCENTIS 0.3 mg)

4 CONTRAINDICATIONS

4.1 Ocular or Periocular Infections

LUCENTIS is contraindicated in patients with ocular or periocular infections.

4.2 Hypersensitivity

LUCENTIS is contraindicated in patients with known hypersensitivity to ranibizumab or any of the excipients in LUCENTIS. Hypersensitivity reactions may manifest as severe intraocular inflammation.

5 WARNINGS AND PRECAUTIONS

5.1 Endophthalmitis and Retinal Detachments

Intravitreal injections, including those with LUCENTIS, have been associated with endophthalmitis and retinal detachments. Proper aseptic injection technique should always be used when administering LUCENTIS. In addition, patients should be monitored during the week following the injection to permit early treatment should an infection occur [*see Dosage and Administration (2.54, 2.65) and Patient Counseling Information (17)*].

5.2 Increases in Intraocular Pressure

Increases in intraocular pressure have been noted within 60 minutes of intravitreal injection with LUCENTIS. Therefore, intraocular pressure as well as the perfusion of the optic nerve head should be monitored and managed appropriately [*see Dosage and Administration (2.65)*].

5.3 Thromboembolic Events

Although there was a low rate of arterial thromboembolic events (ATEs) observed in the LUCENTIS clinical trials, there is a potential risk of ATEs following intravitreal use of VEGF

inhibitors. ATEs are defined as nonfatal stroke, nonfatal myocardial infarction, or vascular death (including deaths of unknown cause).

Neovascular (Wet) Age-Related Macular Degeneration

The ATE rate in the three controlled neovascular AMD studies during the first year was 1.9% (17 ~~out~~ of 874) in the combined group of patients treated with 0.3 mg or 0.5 mg LUCENTIS compared with 1.1% (5 ~~out~~ of 441) in patients from the control arms [*see Clinical Studies (14.1)*]. In the second year of ~~s~~Studies AMD-1 and AMD-2, the ATE rate was 2.6% (19 ~~out~~ of 721) in the combined group of LUCENTIS-treated patients compared with 2.9% (10 ~~out~~ of 344) in patients from the control arms.

In a pooled analysis of 2-year controlled studies (AMD-1, AMD-2, and a study of LUCENTIS used adjunctively with verteporfin photodynamic therapy), the stroke rate (including both ischemic and hemorrhagic stroke) was 2.7% (13 ~~out~~ of 484) in patients treated with 0.5 mg LUCENTIS compared to 1.1% (5 ~~out~~ of 435) in patients in the control arms (odds ratio 2.2 (95% confidence interval (0.8–7.1))).

Macular Edema Following Retinal Vein Occlusion

Patients who had a stroke or myocardial infarction within 3 months prior to study entry were excluded from participation in the two controlled RVO studies [*see Clinical Studies (14.2)*]. The ATE rate in the two controlled RVO studies during the first six months was 0.8% in both the LUCENTIS and control arms of the studies (4 ~~out~~ of 525 in the combined group of patients treated with 0.3 mg or 0.5 mg LUCENTIS and 2 ~~out~~ of 260 in the control arms) ~~[*see Clinical Studies (14.2)*]~~. The stroke rate was 0.2% (1 ~~out~~ of 525) in the combined group of LUCENTIS-treated patients compared to 0.4% (1 ~~out~~ of 260) in the control arms.

Diabetic Macular Edema

Patients who had a stroke or myocardial infarction within 3 months prior to study entry were excluded from participation in the controlled DME-1 and DME-2 studies [*see Clinical Studies (14.3)*]. In a pooled analysis of Studies DME-1 and DME-2, the ATE rate at 2 years was 7.2% (18 of 250) with 0.5 mg LUCENTIS, 5.6% (14 of 250) with 0.3 mg LUCENTIS, and 5.2% (13 of 250) with control. The stroke rate at 2 years was 3.2% (8 of 250) with 0.5 mg LUCENTIS, 1.2% (3 of 250) with 0.3 mg LUCENTIS, and 1.6% (4 of 250) with control. At 3 years, the ATE rate was 10.4% (26 of 249) with 0.5 mg LUCENTIS and 10.8% (27 of 250) with 0.3 mg LUCENTIS; the stroke rate was 4.8% (12 of 249) with 0.5 mg LUCENTIS and 2.0% (5 of 250) with 0.3 mg LUCENTIS.

5.4. Fatal Events in DME Patients

In a pooled analysis of Studies DME-1 and DME-2 [*see Clinical Studies (14.3)*], fatalities in the first 2 years occurred in 4.4% (11 of 250) of patients treated with 0.5 mg LUCENTIS, in 2.8% (7 of 250) of patients treated with 0.3 mg LUCENTIS, and in 1.2% (3 of 250) of control patients. Over 3 years, fatalities occurred in 6.4% (16 of 249) of patients treated with 0.5 mg LUCENTIS and in 4.4% (11 of 250) of patients treated with 0.3 mg LUCENTIS. Although causes of death were those typical of patients with advanced diabetic complications, a potential relationship between these events and intravitreal use of VEGF inhibitors cannot be excluded.

6 ADVERSE REACTIONS

~~Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in one clinical trial of a drug cannot be directly compared with rates in the clinical trials of the same or another drug and may not reflect the rates observed in practice.~~

The following serious adverse reactions are discussed in greater detail in the *Warnings and Precautions (5)* section of the label:

- Endophthalmitis and Retinal Detachments
- Increases in Intraocular Pressure
- Thromboembolic Events
- Fatal Events in DME Patients

6.1 Injection Procedure

Serious adverse reactions related to the injection procedure have occurred in <0.1% of intravitreal injections, including endophthalmitis [*see Warnings and Precautions (5.1)*], rhegmatogenous retinal detachments, and iatrogenic traumatic cataract~~s~~.

6.2 Clinical Studies Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in one clinical trial of a drug cannot be directly compared with rates in the clinical trials of the same or another drug and may not reflect the rates observed in practice.

All studies were randomized, double-masked, and controlled. While some patients received LUCENTIS injections in both eyes, the studies were not designed to investigate the safety of bilateral dosing. Bilateral dosing may lead to increased systemic exposure, which could increase the risk of systemic adverse events [*see Warnings and Precautions (5.3, 5.4)*].

The data below reflect exposure to 0.5 mg LUCENTIS in 440 patients with neovascular AMD ~~in three double-masked, controlled studies (AMD-1, AMD-2, and AMD-3) [*see Clinical Studies (14.1)*] as well as exposure to 0.5 mg LUCENTIS in~~ and 259 patients with macular edema following RVO. The data also reflect exposure to 0.3 mg LUCENTIS in 250 patients with DME [*see Clinical Studies (14)*]. ~~in two double-masked, controlled studies (RVO-1 and RVO-2) [*see Clinical Studies (14.2)*].~~

Ocular Reactions

Table 1 shows frequently reported ocular adverse reactions in LUCENTIS~~-~~-treated patients compared with the control group.

Table 1
Ocular Reactions in the AMD, DME, and RVO Studies

Adverse Reaction	AMD 2-year		AMD 1-year		DME 2-year		RVO 6-month	
	LUCENTIS – 0.5 mg n=379	Control n=379	LUCENTIS – 0.5 mg n=440	Control n=441	LUCENTIS – 0.3 mg n=250	Control n=250	LUCENTIS – 0.5 mg n=259	Control n=260
Conjunctival hemorrhage	74%	60%	64%	50%	47%	32%	48%	37%
Eye pain	35%	30%	26%	20%	17%	13%	17%	12%
Vitreous floaters	27%	8%	19%	5%	10%	4%	7%	2%
Intraocular pressure increased	24%	7%	17%	5%	18%	7%	7%	2%
Vitreous detachment	21%	19%	15%	15%	11%	15%	4%	2%
Intraocular inflammation	18%	8%	13%	7%	4%	3%	1%	3%
Cataract	17%	14%	11%	9%	28%	32%	2%	2%
Foreign body sensation in eyes	16%	14%	13%	10%	10%	5%	7%	5%
Eye irritation	15%	15%	13%	12%	8%	5%	7%	6%
Lacrimation increased	14%	12%	8%	8%	5%	4%	2%	3%
Blepharitis	12%	8%	8%	5%	3%	2%	0%	1%
Dry eye	12%	7%	7%	7%	5%	3%	3%	3%
Visual disturbance or vision blurred	18%	15%	13%	10%	8%	4%	5%	3%
Eye pruritis	12%	11%	9%	7%	4%	4%	1%	2%
Ocular hyperemia	11%	8%	7%	4%	9%	9%	5%	3%
Retinal disorder	10%	7%	8%	4%	2%	2%	2%	1%
Maculopathy	9%	9%	6%	6%	5%	7%	11%	7%
Retinal degeneration	8%	6%	5%	3%	1%	0%	1%	0%
Ocular discomfort	7%	4%	5%	2%	2%	1%	2%	2%
Conjunctival hyperemia	7%	6%	5%	4%	1%	2%	0%	0%
Posterior capsule opacification	7%	4%	2%	2%	4%	3%	0%	1%
Injection site hemorrhage	5%	2%	3%	1%	1%	0%	0%	0%

Non-Ocular Reactions

Table 2 shows frequently reported non-ocular adverse reactions in LUCENTIS--treated neovascular AMD and RVO patients compared with the control group.

Table 2
Non-Ocular Reactions in AMD and RVO Studies

Adverse Reaction	AMD 2-year		AMD 1-year		RVO 6-month	
	Lucentis 0.5 mg n=379	Control n=379	Lucentis 0.5 mg n=440	Control n=441	Lucentis 0.5 mg n=259	Control n=260
Nasopharyngitis	16%	13%	8%	9%	5%	4%
Headache	12%	9%	6%	5%	3%	3%
Arthralgia	11%	9%	5%	5%	2%	1%
Bronchitis	11%	9%	6%	5%	0%	2%
Urinary tract infection	9%	9%	5%	5%	1%	2%
Cough	9%	8%	5%	4%	2%	2%
Nausea	9%	6%	5%	5%	1%	2%
Upper respiratory tract infection	9%	8%	5%	5%	2%	2%
Sinusitis	8%	7%	5%	5%	3%	2%
Anemia	8%	7%	4%	3%	1%	1%
Influenza	7%	5%	3%	2%	3%	2%
Chronic obstructive pulmonary disease	6%	3%	1%	0%	0%	0%
Hypercholesterolemia	5%	5%	3%	2%	1%	1%
Insomnia	5%	5%	3%	2%	1%	1%
Pain in extremity	5%	6%	3%	2%	1%	1%
Atrial fibrillation	5%	4%	2%	2%	1%	0%
Anxiety	4%	4%	3%	2%	1%	2%
Dyspnea	4%	3%	2%	2%	0%	0%
Gastroenteritis viral	4%	1%	3%	1%	1%	0%

Table 3 shows non-ocular adverse reactions which occurred in ≥ 5% of LUCENTIS-treated DME patients for which the incidence was higher in the LUCENTIS 0.3 mg group compared to the control group.

Table 3
Non-Ocular Reactions in the
DME Studies through Year 2

Adverse Reaction	DME 2-year	
	LUCENTIS 0.3 mg	Control
	n=250	n=250
Anemia	11%	10%
Nasopharyngitis	12%	6%
Nausea	10%	9%
Cough	9%	4%
Constipation	8%	4%
Influenza	7%	3%
Seasonal Allergy	8%	4%
Hypercholesterolemia	7%	5%
Renal Failure	7%	6%
Gastrooesophageal Reflux Disease	6%	4%
Edema Peripheral	6%	4%
Coronary Artery Disease	4%	3%
Renal Failure, Chronic	6%	2%
Peripheral Neuropathy	5%	3%

6.3 Immunogenicity

As with all therapeutic proteins, there is the potential for an immune response in patients treated with LUCENTIS. The immunogenicity data reflect the percentage of patients whose test results were considered positive for antibodies to LUCENTIS in immunoassays and are highly dependent on the sensitivity and specificity of the assays.

The pre-treatment incidence of immunoreactivity to LUCENTIS was 0%–5% across treatment groups. After monthly dosing with LUCENTIS for 6 to 24 months, antibodies to LUCENTIS were detected in approximately 1%–8% of patients.

The clinical significance of immunoreactivity to LUCENTIS is unclear at this time. Among neovascular AMD patients with the highest levels of immunoreactivity, some were noted to have iritis or vitritis. Intraocular inflammation was not observed in ~~the~~ RVO or DME patients with the highest levels of immunoreactivity.

7 DRUG INTERACTIONS

Drug interaction studies have not been conducted with LUCENTIS.

LUCENTIS intravitreal injection has been used adjunctively with verteporfin photodynamic therapy (PDT). Twelve of 105 (11%) patients with neovascular AMD developed serious intraocular

inflammation; in 10 of the 12 patients, this occurred when LUCENTIS was administered 7 days (±2 days) after verteporfin PDT.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C. Animal reproduction studies have not been conducted with ranibizumab. It is also not known whether ranibizumab can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. LUCENTIS should be given to a pregnant woman only if clearly needed.

8.3 Nursing Mothers

It is not known whether ranibizumab is excreted in human milk. Because many drugs are excreted in human milk, and because the potential for absorption and harm to infant growth and development exists, caution should be exercised when LUCENTIS is administered to a nursing woman.

8.4 Pediatric Use

The safety and effectiveness of LUCENTIS in pediatric patients has not been established.

8.5 Geriatric Use

In the clinical studies, approximately 72% (1366 of 1908)~~82% (1146/1406)~~ of ~~the~~ patients randomized to treatment with LUCENTIS were ≥65 years of age and approximately 43% (822 of 1908)~~55% (772/1406)~~ were ≥75 years of age [*see Clinical Studies (14)*]. No notable differences in efficacy or safety were seen with increasing age in these studies. Age did not have a significant effect on systemic exposure. ~~in population pharmacokinetic analyses after correcting for creatinine clearance.~~

8.6 Patients with Renal Impairment

No formal studies have been conducted to examine the pharmacokinetics of ranibizumab in patients with renal impairment. In pharmacokinetic covariate analyses, 48% (520/1091) of patients~~population pharmacokinetic analyses of patients, 54% (389/725)~~ had renal impairment (35% mild, 11% moderate, and 2% severe). ~~(39% mild, 12% moderate, and 2% severe).~~ Dose adjustment is not expected to be needed as differences in clearance of or systemic exposure to ranibizumab are considered clinically insignificant in patients with renal impairment.~~The reduction in ranibizumab clearance in patients with renal impairment is considered clinically insignificant. Dose adjustment is not expected to be needed for patients with renal impairment.~~

8.7 Patients with Hepatic Dysfunction

No formal studies have been conducted to examine the pharmacokinetics of ranibizumab in patients with hepatic impairment. Dose adjustment is not expected to be needed for patients with hepatic dysfunction.

10 OVERDOSAGE

Planned initial single doses of ranibizumab injection 1 mg were associated with clinically significant intraocular inflammation in 2 of 2 neovascular AMD patients injected. With an escalating regimen of doses beginning with initial doses of ranibizumab injection 0.3 mg, doses as high as 2 mg were tolerated in 15 of 20 neovascular AMD patients.

11 DESCRIPTION

LUCENTIS® (ranibizumab injection) is a recombinant humanized IgG1 kappa isotype monoclonal antibody Fab fragment (lacking an Fc region), which is designed for intraocular use. Ranibizumab binds to and inhibits the biologic activity of human vascular endothelial growth factor A (VEGF-A). Ranibizumab has a molecular weight of approximately 48 kilodaltons and is produced by an *E. coli* expression system in a nutrient medium containing the antibiotic tetracycline. Tetracycline is not detectable in the final product.

LUCENTIS is a sterile, colorless to pale yellow solution in a single-use glass vial. LUCENTIS is supplied as a preservative-free, sterile solution in a single-use glass vial designed to deliver 0.05 mL of 10 mg/mL LUCENTIS (0.5 mg dose vial) or 6 mg/mL LUCENTIS (0.3 mg dose vial) aqueous solution with 10 mM histidine HCl, 10% α,α-trehalose dihydrate, 0.01% polysorbate 20, pH 5.5.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Ranibizumab binds to the receptor binding site of active forms of VEGF-A, including the biologically active, cleaved form of this molecule, $VEGF_{110}$. VEGF-A has been shown to cause neovascularization and leakage in models of ocular angiogenesis and vascular occlusion, and is thought to contribute to pathophysiology in~~the progression of~~ neovascular AMD, ~~and~~ macular edema following RVO, and DME. The binding of ranibizumab to VEGF-A prevents the interaction of VEGF-A with its receptors (VEGFR1 and VEGFR2) on the surface of endothelial cells, reducing endothelial cell proliferation, vascular leakage, and new blood vessel formation.

12.2 Pharmacodynamics

Increased center point thickness (CPT) as assessed by optical coherence tomography (OCT) is associated with neovascular AMD, ~~and~~ macular edema following RVO, and DME. Leakage from choroidal neovascularization (CNV) as assessed by fluorescein angiography (FA) is associated with neovascular AMD. Vascular leakage, as assessed by FA, and retinal thickening, as assessed by color fundus photography (FP), are associated with DME.

Neovascular (Wet) Age-Related Macular Degeneration

In Study AMD-3, CPT was assessed by OCT in 118 of ~~/~~184 patients. OCT measurements were collected at baseline, Months 1, 2, 3, 5, 8, and 12. In patients treated with LUCENTIS, CPT decreased, on average, more than in the sham group from baseline through Month 12. CPT decreased by Month 1 and decreased further at Month 3, on average. CPT data did not provide information useful in influencing treatment decisions [*see Clinical Studies (14.1)*].

In patients treated with LUCENTIS, the area of vascular leakage, on average, decreased by Month 3 as assessed by FA~~fluorescein angiography~~. The area of vascular leakage for an individual patient was not correlated with visual acuity.

Macular Edema Following Retinal Vein Occlusion

On average, CPT reductions were observed in Studies RVO-1 and RVO-2 beginning at Day 7 following the first LUCENTIS injection through Month 6. CPT was not evaluated as a means to guide treatment decisions [*see Clinical Studies (14.2)*].

Diabetic Macular Edema

On average, CPT reductions were observed in Studies DME-1 and DME-2 beginning at Day 7 following the first LUCENTIS injection through Month 36. CPT was not evaluated in these studies as a means to guide treatment decisions [*see Clinical Studies (14.3)*].

Reductions in the area of vascular leakage on FA and retinal thickening on FP were also observed beginning at Month 3 (the first post-treatment assessment) through Month 36.

12.3 Pharmacokinetics

In animal studies, following intravitreal injection, ranibizumab was cleared from the vitreous with a half-life of approximately 3 days. After reaching a maximum at approximately 1 day, the serum concentration of ranibizumab declined in parallel with the vitreous concentration. In these animal studies, systemic exposure of ranibizumab was~~is~~ more than 2000-fold lower than in the vitreous.

In patients with neovascular AMD, following monthly intravitreal administration, maximum ranibizumab serum concentrations were low (0.3 ng/mL to 2.36 ng/mL). These levels were below the concentration of ranibizumab (11 ng/mL to 27 ng/mL) thought to be necessary to inhibit the biological activity of VEGF-A by 50%, as measured in an in vitro cellular proliferation assay. The maximum observed serum concentration was dose proportional over the dose range of 0.05 to 1 mg/eye. Serum ranibizumab concentrations in RVO and DME patients were similar to those observed in neovascular AMD patients.

Based on a population pharmacokinetic analysis of patients with neovascular AMD, ~~population pharmacokinetic analysis,~~ maximum serum concentrations of 1.5 ng/mL are predicted to be reached at approximately 1 day after monthly intravitreal administration of LUCENTIS 0.5 mg/eye. Based on the disappearance of ranibizumab from serum, the estimated average vitreous elimination half-life was approximately 9 days. Steady-state minimum concentration is predicted to be 0.22 ng/mL with a monthly dosing regimen. In humans, serum ranibizumab concentrations are predicted to be approximately 90,000-fold lower than vitreal concentrations.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No carcinogenicity or mutagenicity data are available for ranibizumab injection in animals or humans.

No studies on the effects of ranibizumab on fertility have been conducted.

14 CLINICAL STUDIES

14.1 Neovascular (Wet) Age-Related Macular Degeneration (AMD)

The safety and efficacy of LUCENTIS were assessed in three randomized, double-masked, sham- or active-controlled studies in patients with neovascular AMD. A total of 1323 patients (LUCENTIS 879, ~~C~~control 444) were enrolled in the three studies.

Studies AMD-1 and AMD-2

In Study AMD-1, patients with minimally classic or occult (without classic) CNV lesions received monthly LUCENTIS 0.3 mg or 0.5 mg intravitreal injections or monthly sham injections. Data are available through Month 24. Patients treated with LUCENTIS in Study AMD-1 received a mean of 22 total treatments out of a possible 24 from Day 0 to Month 24.

In Study AMD-2, patients with predominantly classic CNV lesions received one of the following: 1) monthly LUCENTIS 0.3 mg intravitreal injections and sham PDT; 2) monthly LUCENTIS 0.5 mg intravitreal injections and sham PDT; or 3) sham intravitreal injections and active verteporfin PDT. Sham PDT (or active verteporfin PDT) was given with the initial LUCENTIS (or sham) intravitreal injection and every 3 months thereafter if fluorescein angiography showed persistence or recurrence of leakage. Data are available through Month 24. Patients treated with LUCENTIS in Study AMD-2 received a mean of 21 total treatments out of a possible 24 from Day 0 through Month 24.

In both studies, the primary efficacy endpoint was the proportion of patients who maintained vision, defined as losing fewer than 15 letters of visual acuity at 12 months compared with baseline. Almost all LUCENTIS-treated patients (approximately 95%) maintained their visual acuity. 34%–40% of LUCENTIS-treated patients experienced a clinically significant improvement in vision, defined as gaining 15 or more letters at 12 months. The size of the lesion did not significantly affect the results. Detailed results are shown in the Table 4~~3~~, Table 5~~4~~, and Figure 1 below.

Table 4~~3~~

Outcomes at Month 12 and Month 24 in Study AMD-1

Outcome Measure	Month	Sham n=238	LUCENTIS 0.5 mg n=240	Estimated Difference (95% CI)[a]
Loss of <15 letters in visual acuity (%)[b]	12	62%	95%	32% (26%, 39%)
	24	53%	90%	37% (29%, 44%)
Gain of ≥15 letters in visual acuity (%)[b]	12	5%	34%	29% (22%, 35%)
	24	4%	33%	29% (23%, 35%)
Mean change in visual acuity (letters) (SD)[b]	12	−10.5 (16.6)	+7.2 (14.4)	17.5 (14.8, 20.2)
	24	−14.9 (18.7)	+6.6 (16.5)	21.1 (18.1, 24.2)

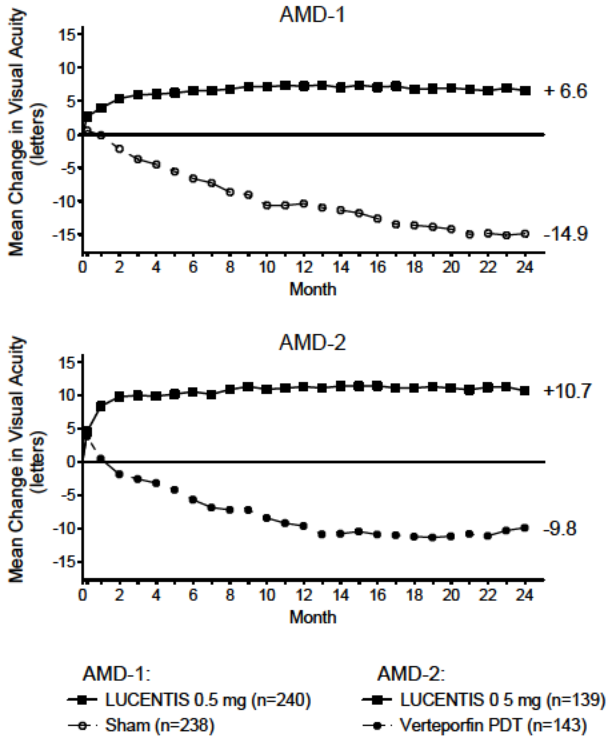
[a] Adjusted estimate based on the stratified model; [b] p<0.01.

Table 54
Outcomes at Month 12 and Month 24 in Study AMD-2

Outcome Measure	Month	Verteporfin PDT n=143	LUCENTIS 0.5 mg n=139	Estimated Difference (95% CI)[a]
Loss of <15 letters in visual acuity (%)[b]	12	64%	96%	33% (25%, 41%)
	24	66%	90%	25% (16%, 34%)
Gain of ≥15 letters in visual acuity (%)[b]	12	6%	40%	35% (26%, 44%)
	24	6%	41%	35% (26%, 44%)
Mean change in visual acuity (letters) (SD)[b]	12	–9.5 (16.4)	+11.3 (14.6)	21.1 (17.5, 24.6)
	24	–9.8 (17.6)	+10.7 (16.5)	20.7 (16.8, 24.7)

[a] Adjusted estimate based on the stratified model; [b] p<0.01.

Figure 1
Mean Change in Visual Acuity from Baseline to Month 24 in Study AMD-1 and Study AMD-2



Patients in the group treated with LUCENTIS had minimal observable CNV lesion growth, on average. At Month 12, the mean change in the total area of the CNV lesion was 0.1–0.3 disc areas (DA) for LUCENTIS versus 2.3–2.6 DA for the control arms. At Month 24, the mean change in the total area of the CNV lesion was 0.3–0.4 DA for LUCENTIS versus 2.9–3.1 DA for the control arms.

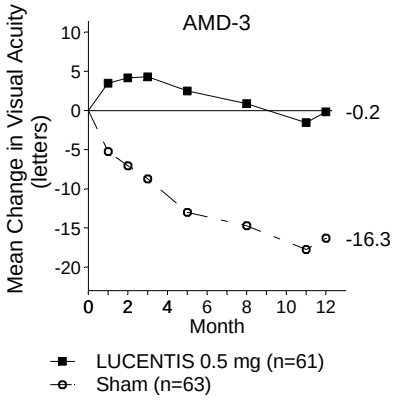
Study AMD-3

Study AMD-3 was a randomized, double-masked, sham-controlled, two-year study designed to assess the safety and efficacy of LUCENTIS in patients with neovascular AMD (with or without a classic CNV component). Data are available through Month 12. Patients received LUCENTIS 0.3 mg or 0.5 mg intravitreal injections or sham injections once a month for 3 consecutive doses, followed by a dose administered once every 3 months for 9 months. A total of 184 patients were enrolled in this study (LUCENTIS 0.3 mg, 60; LUCENTIS 0.5 mg, 61; sham, 63); 171 (93%) completed 12 months of this study. Patients treated with LUCENTIS in Study AMD-3 received a mean of 6 total treatments out of a possible 6 from Day 0 through Month 12.

In Study AMD-3, the primary efficacy endpoint was mean change in visual acuity at 12 months compared with baseline (see Figure 2). After an initial increase in visual acuity (following monthly dosing), on average, patients dosed once every three months with LUCENTIS lost visual acuity, returning to baseline at Month 12. In Study AMD-3, almost all LUCENTIS-treated patients (90%) maintained their visual acuity at Month 12.

Figure 2

Mean Change in Visual Acuity from Baseline to Month 12 in Study AMD-3



14.2 Macular Edema Following Retinal Vein Occlusion (RVO)

The safety and efficacy of LUCENTIS were assessed in two randomized, double-masked, one-year studies in patients with macular edema following RVO. Sham controlled data are available through Month 6. Patient age ranged from 20 to 91 years, with a mean age of 67 years. A total of 789 patients (LUCENTIS 0.3 mg, 266 patients; LUCENTIS 0.5 mg, 261 patients; sham, 262 patients) were enrolled, with 739 (94%) patients completing through Month 6. Patients who experienced a stroke or myocardial infarction within 3 months prior to study entry were excluded from participation. All patients completing Month 6 were eligible to receive LUCENTIS injections guided by pre-specified re-treatment criteria until the end of the studies at Month 12.

In Study RVO-1, patients with macular edema following branch or hemi-RVO, received monthly LUCENTIS 0.3 mg or 0.5 mg intravitreal injections or monthly sham injections for 6 months. All patients were eligible for macular focal/grid~~rescue~~ laser treatment beginning at Month 3 of the 6 month treatment period. Macular focal/grid~~Rescue~~ laser treatment was given to 26 of 131 (20%) patients treated with 0.5 mg LUCENTIS and 712 of 132 (545%) patients treated with sham.

In Study RVO-2, patients with macular edema following central RVO received monthly LUCENTIS 0.3 mg or 0.5 mg intravitreal injections or monthly sham injections for 6 months.

At Month 6, after monthly treatment with 0.5 mg LUCENTIS, the following clinical results were observed:

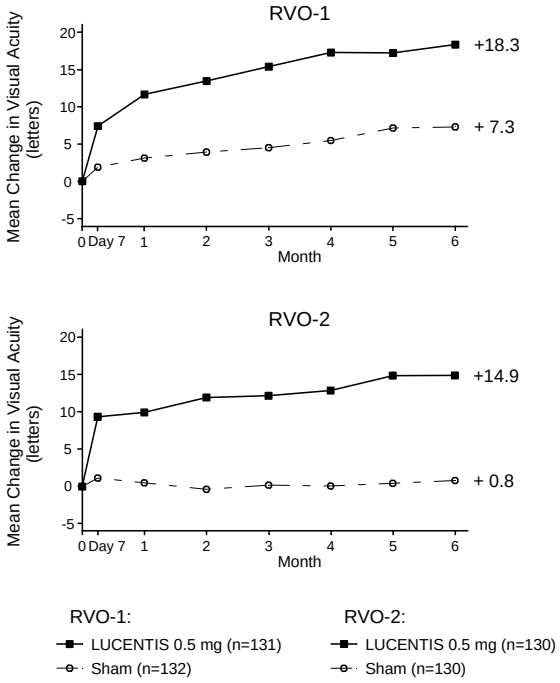
Table 65

Percentage of Patients with Gain of ≥15 letters in Visual Acuity from Baseline to Month 6 in Study RVO-1 and Study RVO-2

Study	Sham	LUCENTIS 0.5 mg	Estimated Difference (95% CI)
RVO-1	29%	61%	31%[a] (20%, 43%)
RVO-2	17%	48%	30%[a] (20%, 41%)

[a] $p < 0.01$, adjusted estimate based on stratified model.

Figure 3
Mean Change in Visual Acuity from Baseline
to Month 6 in Study RVO-1 and Study RVO-2



p < 0 01 for all time points

14.3 Diabetic Macular Edema (DME)

The safety and efficacy of LUCENTIS were assessed in two randomized, double-masked, three-year studies in patients with DME. The studies were sham-controlled through Month 24. Patient age ranged from 21 to 91 years, with a mean age of 62 years. A total of 759 patients (LUCENTIS 0.3 mg, 250 patients; LUCENTIS 0.5 mg, 252 patients; sham, 257 patients) were enrolled, with 637 (84%) patients completing through Month 24. Patients who had experienced a stroke or myocardial infarction within 3 months prior to study entry were excluded from participation.

In Studies DME-1 and DME-2, patients received monthly LUCENTIS 0.3 mg or 0.5 mg intravitreal injections or monthly sham injections during the 24-month controlled treatment period. From Months 25 through 36, patients who previously received sham were eligible to receive monthly LUCENTIS 0.5 mg and patients originally randomized to monthly LUCENTIS 0.3 mg or 0.5 mg continued to receive their assigned dose. All patients were eligible for macular focal/grid laser treatment beginning at Month 3 of the 24-month treatment period or panretinal photocoagulation (PRP) as needed. Through Month 24, macular focal/grid laser treatment was administered in 94 of 250 (38%) patients treated with LUCENTIS 0.3 mg and 185 of 257 (72%) patients treated with sham; PRP was administered in 2 of 250 (1%) patients treated with LUCENTIS 0.3 mg and 30 of 257 (12%) patients treated with sham.

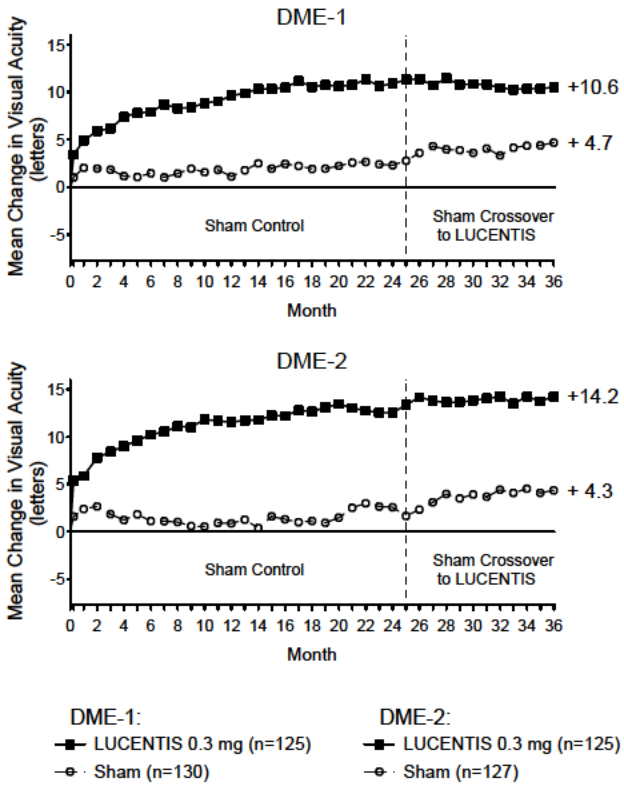
Compared to monthly LUCENTIS 0.3 mg, monthly treatment with LUCENTIS 0.5 mg resulted on average in similar visual acuity (VA) and anatomic outcomes and provided no incremental vision improvement. At Month 24, after monthly treatment with LUCENTIS 0.3 mg, the following clinical results were observed:

Table 7
Visual Acuity Outcomes at Month 24 in Study DME-1 and Study DME-2

Study	Treatment Arm	Gain of ≥ 15 letters (% of patients)	Estimated Difference (95% CI)[a]	Loss of < 15 letters (% of patients)	Estimated Difference (95% CI)[a]	Mean Change in Visual Acuity (letters) from Baseline	Estimated Difference (95% CI)[a]
DME-1	LUCENTIS 0.3 mg	34%	21%[b] (11%, 30%)	98%	7%[c] (2%, 13%)	10.9	8.5[b] (5.4, 11.5)
	Sham	12%	—	92%	—	2.3	—
DME-2	LUCENTIS 0.3 mg	45%	24%[b] (14%, 35%)	98%	8%[c] (2%, 14%)	12.5	9.6[b] (6.1, 13.0)
	Sham	18%	—	90%	—	2.6	—

[a] adjusted estimate based on stratified model; [b] p <0.01; [c] p=0.01.

Figure 4
Mean Change in Visual Acuity from Baseline
to Month 36 in Study DME-1 and Study DME-2



p < 0 01 for all time points comparing LUCENTIS 0 3 mg to sham through Month 24

VA outcomes observed at Month 24 in patients treated with LUCENTIS 0.3 mg were maintained with continued treatment through Month 36 in both DME studies. Patients in the sham arms who received LUCENTIS 0.5 mg beginning at Month 25 achieved lesser VA gains compared to patients who began treatment with LUCENTIS at the beginning of the studies.

VA benefits were observed in all patient subgroups defined by key baseline factors including those defined by baseline Hemoglobin A1c (≤8% or >8%), anatomic type of macular edema (with or without predominantly focal edema), or prior treatment for macular edema.

At Month 24, fewer patients treated with LUCENTIS developed proliferative diabetic retinopathy (0.3 mg, 2%; sham, 13%) or experienced adverse events typical of worsening diabetic retinopathy, such as vitreous hemorrhage (0.3 mg, 2%; sham, 14%). As measured on the ETDRS retinopathy severity scale for eyes, patients treated with LUCENTIS were less likely to progress by ≥3 steps (0.3 mg, 1%; sham, 5%) or ≥2 steps (0.3 mg, 2%; sham, 10%) and more likely to improve by ≥2 steps (0.3 mg, 37%; sham, 5%).

16 HOW SUPPLIED/STORAGE AND HANDLING

Each LUCENTIS 0.5 mg carton~~,~~ (NDC 50242-080-01)~~,~~ contains a single-use, 2-cc glass vial designed to deliver 0.05 mL ~~0.2 mL fill~~ of 10 mg/mL ranibizumab. ~~in a 2 cc glass vial;~~ Each LUCENTIS 0.3 mg carton (NDC 50242-082-01) contains a single-use, 2-cc glass vial designed to deliver 0.05 mL of 6 mg/mL ranibizumab. In addition, each carton contains one 5-micron, 19-gauge × 1-1/2-inch filter needle for withdrawal of the vial contents; one 30-gauge × 1/2-inch injection needle for the intravitreal injection; and one package insert [*see Dosage and Administration (2.6~~5~~)*]. VIALS ARE FOR SINGLE EYE USE ONLY.

LUCENTIS should be refrigerated at 2°–8ºC (36°–46ºF). DO NOT FREEZE. Do not use beyond the date stamped on the label. LUCENTIS vials should be protected from light. Store in the original carton until time of use.

17 PATIENT COUNSELING INFORMATION

In the days following LUCENTIS administration, patients are at risk of developing endophthalmitis. If the eye becomes red, sensitive to light, painful, or develops a change in vision, the patient should seek immediate care from an ophthalmologist [*see Warnings and Precautions (5.1)*].

LUCENTIS® [ranibizumab injection]

Manufactured by:
Genentech, Inc.
A Member of the Roche Group
1 DNA Way
South San Francisco, CA 94080-4990

xxxxxxx~~4851401~~
~~Initial US Approval June 2006~~
~~Revision Date June 2010~~LUCENTIS® is a registered trademark of Genentech, Inc.

Appendix 3 Outcome Measures and Statistical Methods

PRIMARY OUTCOME MEASURE

The primary efficacy outcome measure in RIDE and RISE was the proportion of patients who gained ≥15 letters from baseline best corrected visual acuity (BCVA) score at 24 months.

SECONDARY EFFICACY OUTCOME MEASURES

The following secondary outcome measures were assessed:

- Mean change from baseline in BCVA score over time up to 24 months
- Proportion of patients with a BCVA Snellen equivalent of 20/40 or better at 24 months
- Mean change from baseline in BCVA score over time up to 24 months in patients with focal edema at baseline, as assessed on fluorescein angiography (FA) by the central reading center
- Proportion of patients who lose fewer than 15 letters in BCVA score at 24 months compared with baseline
- Mean change from baseline in central foveal thickness (CFT) over time up to 24 months, as assessed on optical coherence tomography (OCT) by the central reading center
- Proportion of patients with a three-step or greater progression from baseline in the Early Treatment of Diabetic Retinopathy Study (ETDRS) diabetic retinopathy severity level at 24 months, as assessed by the central reading center using fundus photography (FP)
- Proportion of patients with resolution of leakage at 24 months, as assessed by the central reading center using FA
- Mean number of macular laser treatments during 24 months

Additional secondary outcome measures will include the following 36-month outcome measures:

- Proportion of patients who gain at least 15 letters in BCVA score compared with baseline at 36 months
- Mean change from baseline in BCVA score over time up to 36 months
- Proportion of patients with a BCVA Snellen equivalent of 20/40 or better at 36 months
- Mean change from baseline in BCVA score over time up to 36 months in patients with focal edema at baseline, as assessed on FA by the central reading center
- Proportion of patients who lose fewer than 15 letters in BCVA score at 36 months compared with baseline

- Mean change from baseline in CFT over time up to 36 months, as assessed on OCT by the central reading center
- Proportion of patients with a three-step or greater progression from baseline in the ETDRS diabetic retinopathy severity level at 36 months, as assessed by the central reading center using FP
- Mean number of macular laser treatments during 36 months

EXPLORATORY EFFICACY OUTCOME MEASURES

Other pre-specified exploratory efficacy endpoints included:

- Proportion of patients who gain at least 10 letters in BCVA score compared with baseline at 24 months
- Proportion of patients who gain at least 15 letters in BCVA score compared with baseline at Day 7 and Months 1, 3, 6, 12, and 18
- Mean change in BCVA score from Month 18 to Month 24
- Mean change from baseline in contrast sensitivity at 24 months, as measured by the number of letters read correctly on the Pelli-Robson chart
- Proportion of patients with a CFT $\leq$250 μm at 24 months, as assessed on OCT by the central reading center
- Mean change in the area of retinal thickening from baseline to 24 months, as assessed by the central reading center using FP
- Proportion of patients with a $\geq$2-step improvement from baseline in the ETDRS diabetic retinopathy severity level at 24 months, as assessed by the central reading center using FP
- Proportion of patients with a $\geq$2-step progression from baseline in the ETDRS diabetic retinopathy severity level at 24 months, as assessed by the central reading center using FP
- Proportion of patients who receive macular laser treatment during 24 months
- Mean change from baseline in the composite score and the 12 subscale scores of the NEI VFQ-25 at 24 months
- Proportion of patients with less difficulty in “reading ordinary print in newspapers” at 24 months compared with baseline, as assessed on the NEI VFQ-25
  - Less difficulty is defined as a one-category or greater decrease in difficulty level from baseline.
- Mean change in the number of words read per minute on the reading speed assessment from baseline to 24 months (for patients who read English at U.S. sites only)
- Proportion of patients progressing to proliferative diabetic retinopathy (PDR) by Month 24

Additional exploratory outcome measures include the following 36-month outcome measures:

- Proportion of patients who lose fewer than 15 letters in BCVA score at 36 months compared with baseline
- Proportion of patients who gain at least 10 letters in BCVA score compared with baseline at 36 months
- Mean change from baseline in contrast sensitivity at 36 months, as measured by the number of letters read correctly on the Pelli-Robson chart
- Proportion of patients with a CFT $\leq$250 μm at 36 months, as assessed on OCT by the central reading center
- Proportion of patients with a $\geq$2-step improvement from baseline in the ETDRS diabetic retinopathy severity level at 36 months, as assessed by the central reading center using FP
- Proportion of patients with a $\geq$2-step progression from baseline in the ETDRS diabetic retinopathy severity level at 36 months, as assessed by the central reading center using FP
- Proportion of patients who receive macular laser treatment during 36 months
- Proportion of patients progressing to PDR by Month 36

SAFETY ENDPOINTS

- Incidence and severity of ocular adverse events
- Incidence and severity of non-ocular adverse events
- Changes and abnormalities in clinical laboratory parameters
- Incidence of positive serum antibodies to ranibizumab
- Changes in vital signs

STATISTICAL ANALYSIS PLAN

SAMPLE SIZE

Assuming that expected proportions of patients gaining at least 15 letters from baseline at 24 months (the primary endpoint) were 35% for 0.5-mg ranibizumab-treated patients, 25% for 0.3-mg ranibizumab-treated patients, and 13% for sham-treated control patients, a total of 366 patients would provide 90% experiment-wise power to detect these differences. Power was estimated using Monte Carlo simulations under the assumption of a 15% drop-out per year and use of the Hochberg–Bonferroni approach for adjustment of multiple comparisons.

RANDOMIZATION STRATIFICATION FACTORS

Randomization was stratified by baseline BCVA (≤55, >55 letters) in the study eye, glycosylated hemoglobin (HbA_{1c}) (≤8%, >8%), and prior therapy for DME in the study eye (yes or no).

STATISTICAL METHODS

The primary analyses of the efficacy endpoints were performed based on data collected through Month 24 after all patients in RIDE and RISE completed the Month 24 visit or discontinued early from the studies. In addition, 36-month data were analyzed to evaluate maintenance of effect and long-term safety.

Analyses of the efficacy endpoints included all randomized patients (the intent-to-treat [ITT] population) unless otherwise specified. Patients were analyzed according to their randomized treatment assignment. Safety analyses were based on randomized patients who received at least one study treatment (ranibizumab or sham injection) with treatment groups defined according to the actual treatment received.

Comparisons of efficacy were performed between each ranibizumab dose group and the sham-injection (control) group at Month 24. Ad hoc analyses were performed to compare the effect of long-term ranibizumab treatment (0.3-mg and 0.5-mg groups) versus delayed ranibizumab treatment (sham/0.5-mg group) at Month 36. Missing data in the main efficacy analyses were imputed using the last observation carried forward (LOCF) approach.

The primary efficacy endpoint, the proportion of patients who gained ≥15 letters from baseline BCVA score at 24 months, in each ranibizumab group was compared with the control group separately using the Cochran-Mantel–Haenszel chi square test (Landis et al. 1978) stratified by baseline BCVA score (≤55, >55 letters), HbA_{1c} (≤8%, >8%), and prior therapy for DME (yes, no). The Hochberg–Bonferroni multiple comparison procedure was used to adjust for the two pairwise treatment comparisons (Hochberg 1988). The proportion for each treatment group and the overall difference in proportions between treatment groups were estimated by the weighted average of the observed values over the strata using the Cochran–Mantel–Haenszel (CMH) weights (Cochran 1954; Mantel and Haenszel 1959; Mehrota and Railkar 2000). Confidence intervals were calculated using the normal approximation to the binomial distribution.

The other categorical efficacy outcome measures were estimated and the results between treatment groups were compared using the same approach as the primary endpoint. The continuous efficacy endpoints in each ranibizumab group were compared with the control group separately with an ANOVA model adjusting for the baseline strata for BCVA, HbA_{1c}, and prior therapy for DME. To control overall type I error, all secondary endpoints included in the Month 24 analysis were tested in a pre-specified hierarchical order.

MINIMIZATION OF BIAS

To minimize bias, the trial was double-masked using sham injections, and patients were randomized at an approximately 1:1:1 ratio to the three treatment groups using a central interactive voice response system (IVRS). In addition, patients, study site personnel (with the exception of the treating physician[s] and assistant, if needed), the designated evaluating physician(s), and central reading center personnel were masked to a patient's treatment assignment. The Sponsor was also masked prior to the primary analysis.

The investigator performing the ranibizumab or sham injection (and assistant, if needed) was unmasked to treatment assignment (ranibizumab or sham) but was masked to the dose of study drug (0.3 or 0.5 mg). This investigator (and assistant, if needed) was not allowed to be involved in any other aspect of the study (with the exception of administering macular laser treatment to the study eye but not including the assessment to determine whether laser treatment was indicated).

A masked evaluating physician and masked site personnel were responsible for conducting ocular assessments and all other aspects of the study. Both evaluating and treating physicians might administer macular laser therapy to the study eye.

Because Genentech personnel were masked to patients' treatment assignments until the time of the primary analyses, an independent Data Monitoring Committee (iDMC) was chartered and established prior to the beginning of the study to monitor patient safety and conduct. The iDMC had access to unmasked safety and outcomes data by treatment group, prepared by an independent Statistical Coordinating Center. An independent review of anatomical outcomes as measured by optical coherence tomography (OCT), fundus photography (FP), and fluorescein angiography (FA) were performed by a central reading center, which was masked to the treatment assessment.

After the 24-month primary analysis, patients, study site personnel (with the exception of the treating physician[s] and assistant, if needed), and central reading center personnel remained masked to individual treatment assignments.

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Appendix 4 Additional Patient Disposition and Efficacy Tables

Table 4.1 Patient Disposition and Primary Reason for Discontinuation during the 36-Month Treatment Period

	RIDE			RISE			Pooled		
	Sham/ 0.5 mg RBZ (n =130)	0.3 mg RBZ (n =125)	0.5 mg RBZ (n =127)	Sham/ 0.5 mg RBZ (n =127)	0.3 mg RBZ (n =125)	0.5 mg RBZ (n = 125)	Sham/ 0.5 mg RBZ (n = 257)	0.3 mg RBZ (n = 250)	0.5 mg RBZ (n = 252)
Received study drug	127 (97.7%)	125 (100%)	124 (97.6%)	126 (99.2%)	124 (99.2%)	124 (99.2%)	253 (98.4%)	249 (99.6%)	248 (98.4%)
Completed study through Month 24	108 (83.1%)	105 (84.0%)	110 (86.6%)	102 (80.3%)	105 (84.0%)	106 (84.8%)	211 (82.1%)	210 (84.0%)	216 (85.7%)
Completed study through Month 36	102 (78.5%)	98 (78.4%)	98 (77.2%)	86 (67.7%)	98 (78.4%)	100 (80.0%)	188 (73.2%)	196 (78.4%)	198 (78.6%)
Discontinued from the study prior to Month 36									
Total	28 (21.5%)	27 (21.6%)	29 (22.8%)	41 (32.3%)	27 (21.6%)	25 (20.0%)	69 (26.8%)	54 (21.6%)	54 (21.4%)
Adverse event	3 (2.3%)	1 (0.8%)	1 (0.8%)	1 (0.8%)	4 (3.2%)	4 (3.2%)	4 (1.6%)	5 (2.0%)	5 (2.0%)
Death	3 (2.3%)	5 (4.0%)	10 (7.9%)	4 (3.1%)	6 (4.8%)	4 (3.2%)	7 (2.7%)	11 (4.4%)	14 (5.6%)
Lost to follow-up	3 (2.3%)	3 (2.4%)	3 (2.4%)	10 (7.9%)	5 (4.0%)	5 (4.0%)	13 (5.1%)	8 (3.2%)	8 (3.2%)
Physician's decision	1 (0.8%)	2 (1.6%)	2 (1.6%)	3 (2.4%)	2 (1.6%)	1 (0.8%)	4 (1.6%)	4 (1.6%)	3 (1.2%)
Patient non-compliance	5 (3.8%)	2 (1.6%)	1 (0.8%)	1 (0.8%)	1 (0.8%)	2 (1.6%)	6 (2.3%)	3 (1.2%)	3 (1.2%)
Patient's condition mandated other therapeutic intervention	1 (0.8%)	3 (2.4%)	2 (1.6%)	3 (2.4%)	0 (0.0%)	1 (0.8%)	4 (1.6%)	3 (1.2%)	3 (1.2%)
Patient's decision	12 (9.2%)	11 (8.8%)	10 (7.9%)	19 (15.0%)	9 (7.2%)	8 (6.4%)	31 (12.1%)	20 (8.0%)	18 (7.1%)

RBZ=ranibizumab.

Table 4.1 Patient Disposition and Primary Reason for Discontinuation during the 36-Month Treatment Period (cont.)

	RIDE			RISE			Pooled		
	Sham/ 0.5 mg RBZ (n =130)	0.3 mg RBZ (n =125)	0.5 mg RBZ (n =127)	Sham/ 0.5 mg RBZ (n =127)	0.3 mg RBZ (n =125)	0.5 mg RBZ (n = 125)	Sham/ 0.5 mg RBZ (n = 257)	0.3 mg RBZ (n = 250)	0.5 mg RBZ (n = 252)
Discontinued from treatment prior to Month 36									
Total	30 (23.1%)	37 (29.6%)	29 (22.8%)	42 (33.1%)	28 (22.4%)	30 (24.0%)	72 (28.0%)	65 (26.0%)	59 (23.4%)
Adverse event	6 (4.6%)	4 (3.2%)	6 (4.7%)	4 (3.1%)	5 (4.0%)	5 (4.0%)	10 (3.9%)	9 (3.6%)	11 (4.4%)
Death	3 (2.3%)	5 (4.0%)	9 (7.1%)	3 (2.4%)	6 (4.8%)	4 (3.2%)	6 (2.3%)	11 (4.4%)	13 (5.2%)
Lost to follow-up	2 (1.5%)	3 (2.4%)	2 (1.6%)	10 (7.9%)	5 (4.0%)	3 (2.4%)	12 (4.7%)	8 (3.2%)	5 (2.0%)
Physician's decision	0 (0.0%)	2 (1.6%)	0 (0.0%)	2 (1.6%)	1 (0.8%)	2 (1.6%)	2 (0.8%)	3 (1.2%)	2 (0.8%)
Patient non-compliance	3 (2.3%)	2 (1.6%)	1 (0.8%)	1 (0.8%)	1 (0.8%)	2 (1.6%)	4 (1.6%)	3 (1.2%)	3 (1.2%)
Patient's condition mandated other therapeutic intervention	4 (3.1%)	5 (4.0%)	1 (0.8%)	5 (3.9%)	0 (0.0%)	2 (1.6%)	9 (3.5%)	5 (2.0%)	3 (1.2%)
Patient's decision	12 (9.2%)	16 (12.8%)	10 (7.9%)	17 (13.4%)	10 (8.0%)	12 (9.6%)	29 (11.3%)	26 (10.4%)	22 (8.7%)

RBZ=ranibizumab.

Table 4.2 Proportion of Patients Gaining ≥ 15 Letters from Baseline in BCVA Score in the Study Eye at 24 and 36 Months

	RIDE			RISE			Pooled		
	Sham/ 0.5 mg RBZ (n =130)	0.3 mg RBZ (n =125)	0.5 mg RBZ (n =127)	Sham/ 0.5 mg RBZ (n =127)	0.3 mg RBZ (n =125)	0.5 mg RBZ (n = 125)	Sham/ 0.5 mg RBZ (n = 257)	0.3 mg RBZ (n = 250)	0.5 mg RBZ (n = 252)
Month 24									
n (%)	16 (12.3%)	42 (33.6%)	58 (45.7%)	23 (18.1%)	56 (44.8%)	49 (39.2%)	39 (15.2%)	98 (39.2%)	107 (42.5%)
95% CI for percentage a	(6.7%, 18.0%)	(25.3%, 41.9%)	(37.0%, 54.3%)	(11.4%, 24.8%)	(36.1%, 53.5%)	(30.6%, 47.8%)	(10.8%, 19.6%)	(33.1%, 45.3%)	(36.4%, 48.6%)
Difference in % (vs. sham) [b]		20.8%	33.3%		24.3%	20.9%		22.7%	28.1%
95% CI for difference [b]		(11.4%, 30.2%)	(23.8%, 42.8%)		(13.8%, 34.8%)	(10.7%, 31.1%)		(15.5%, 30.0%)	(21.0%, 35.1%)
P-value (vs. sham)		< 0.0001	< 0.0001		0.0002	< 0.0001		< 0.0001	< 0.0001
Month 36									
n (%)	25 (19.2%)	46 (36.8%)	51 (40.2%)	28 (22.0%)	64 (51.2%)	52 (41.6%)	53 (20.6%)	110 (44.0%)	103 (40.9%)
95% CI for percentage [a]	(12.5%, 26.0%)	(28.3%, 45.3%)	(31.6%, 48.7%)	(14.8%, 29.3%)	(42.4%, 60.0%)	(33.0%, 50.2%)	(15.7%, 25.6%)	(37.8%, 50.2%)	(34.8%, 46.9%)
Difference in % (vs. sham) [b]		16.9%	20.8%		26.6%	20.0%		21.8%	21.1%
95% CI for difference [b]		(6.8%, 27.0%)	(10.9%, 30.8%)		(15.7%, 37.5%)	(9.4%, 30.6%)		(14.2%, 29.4%)	(13.7%, 28.5%)
P-value (vs. sham)		0.0026	0.0001		<0.0001	0.0005		< 0.0001	< 0.0001

RBZ =ranibizumab.

Notes: The last observation carried forward (LOCF) method was used to impute missing data.

Strata were defined using baseline BCVA score (≤ 55, > 55 letters), baseline HbA1c level (≤ 8%, > 8%), and prior therapy for DME in the study eye (yes, no).

[a] By normal approximation of the observed proportions.

[b] Weighted estimates adjusted for the baseline strata using Cochran–Mantel–Haenszel weights and normal approximation of the weighted estimates.

Table 4.3 Mean Change in BCVA Score from Baseline in the Study Eye at 24 and 36 Months

	RIDE			RISE			Pooled		
	Sham/ 0.5 mg RBZ (n=130)	0.3 mg RBZ (n=125)	0.5 mg RBZ (n=127)	Sham/ 0.5 mg RBZ (n=127)	0.3 mg RBZ (n=125)	0.5 mg RBZ (n=125)	Sham/ 0.5 mg RBZ (n=257)	0.3 mg RBZ (n=250)	0.5 mg RBZ (n=252)
Month 24									
Mean (SD)	2.3 (14.2)	10.9 (10.4)	12.0 (14.9)	2.6 (13.9)	12.5 (14.1)	11.9 (12.1)	2.5 (14.0)	11.7 (12.4)	12.0 (13.6)
95% CI for mean [a]	(–0.1, 4.8)	(9.1, 12.8)	(9.4, 14.7)	(0.1, 5.0)	(10.0, 15.0)	(9.8, 14.1)	(0.7, 4.2)	(10.2, 13.3)	(10.3, 13.7)
Difference in LS means (vs. sham) [b]		8.5	9.9		9.6	9.4		9.0	9.7
95% CI for difference [b]		(5.4,11.5)	(6.4,13.3)		(6.1,13.0)	(6.2,12.6)		(6.8,11.3)	(7.4,12.1)
P-value (vs. sham)		< 0.0001	< 0.0001		< 0.0001	< 0.0001		< 0.0001	< 0.0001
Month 36									
Mean (SD)	4.7 (13.3)	10.6 (12.9)	11.4 (16.3)	4.3 (14.9)	14.2 (12.8)	11.0 (12.9)	4.5 (14.1)	12.4 (13.0)	11.2 (14.7)
95% CI for mean [a]	(2.4, 7.0)	(8.3, 12.8)	(8.6, 14.3)	(1.7, 7.0)	(12.0, 16.5)	(8.8, 13.3)	(2.8, 6.3)	(10.8, 14.0)	(9.4, 13.1)
Difference in LS means (vs. sham) [b]		5.8	6.9		9.4	6.8		7.6	6.9
95% CI for difference [b]		(2.6, 9.0)	(3.4,10.5)		(6.0,12.8)	(3.4,10.1)		(5.3, 9.9)	(4.4, 9.3)
P-value (vs. sham)		0.0005	0.0001		< 0.0001	0.0001		< 0.0001	< 0.0001

RBZ =ranibizumab.

Notes: The last observation carried forward (LOCF) method was used to impute missing data.

Strata were defined using baseline BCVA score (≤ 55, > 55 letters), baseline HbA1c level (≤ 8%, > 8%), and prior therapy for DME in the study eye (yes, no).

[a] Based on the t-distribution.

[b] Based on pairwise ANOVA models adjusted for the baseline strata.

Table 4.4 Proportion of Patients Losing < 15 Letters from Baseline in BCVA Score in the Study Eye at 24 Months and 36 Months

	RIDE			RISE			Pooled		
	Sham/ 0.5 mg RBZ (n =130)	0.3 mg RBZ (n =125)	0.5 mg RBZ (n =127)	Sham/ 0.5 mg RBZ (n =127)	0.3 mg RBZ (n =125)	0.5 mg RBZ (n = 125)	Sham/ 0.5 mg RBZ (n = 257)	0.3 mg RBZ (n = 250)	0.5 mg RBZ (n = 252)
Month 24									
n (%)	119 (91.5%)	123 (98.4%)	122 (96.1%)	114 (89.8%)	122 (97.6%)	122 (97.6%)	233 (90.7%)	245 (98.0%)	244 (96.8%)
95% CI for percentage a	(86.8%, 96.3%)	(96.2%, 100%)	(92.7%, 99.4%)	(84.5%, 95.0%)	(94.9%, 100%)	(94.9%, 100%)	(87.1%, 94.2%)	(96.3%, 99.7%)	(94.7%, 99.0%)
Difference in % (vs. sham) [b]		7.1%	4.5%		8.2%	7.8%		7.8%	6.4%
95% CI for difference [b]		(1.7%, 12.6%)	(–1.2%, 10.1%)		(2.4%, 14.1%)	(2.0%, 13.6%)		(3.8%, 11.9%)	(2.2%, 10.6%)
P-value		0.0119	0.1384		0.0086	0.0126		0.0002	0.0033
Month 36									
n (%)	120 (92.3%)	121 (96.8%)	122 (96.1%)	116 (91.3%)	124 (99.2%)	122 (97.6%)	236 (91.8%)	245 (98.0%)	244 (96.8%)
95% CI for percentage [a]	(87.7%, 96.9%)	(93.7%, 99.9%)	(92.7%, 99.4%)	(86.4%, 96.2%)	(97.6%, 100%)	(94.9%, 100%)	(88.5%, 95.2%)	(96.3%, 99.7%)	(94.7%, 99.0%)
Difference in % (vs. sham) [b]		3.9%	3.8%		7.5%	6.0%		5.9%	5.0%
95% CI for difference [b]		(–1.8%, 9.6%)	(–1.7%, 9.3%)		(2.9%, 12.1%)	(0.9%, 11.2%)		(2.2%, 9.6%)	(1.1%, 9.0%)
P-value		0.1853	0.1959		0.0055	0.0386		0.0030	0.0137

RBZ =ranibizumab. Notes: The last observation carried forward (LOCF) method was used to impute missing data.

Strata were defined using baseline BCVA score (≤ 55, > 55 letters), baseline HbA_{1c} level (≤ 8%, > 8%), and prior therapy for DME in the study eye (yes, no).

[a] By normal approximation of the observed proportions.

[b] Weighted estimates adjusted for the baseline strata using Cochran–Mantel–Haenszel weights and normal approximation of the weighted estimates.

Table 4.5 Mean Change in Central Foveal Thickness from Baseline in the Study Eye at 24 and 36 Months

Change from Baseline (µm)	RIDE			RISE			Pooled		
	Sham/ 0.5 mg RBZ (n=130)	0.3 mg RBZ (n=125)	0.5 mg RBZ (n=127)	Sham/ 0.5 mg RBZ (n=127)	0.3 mg RBZ (n=125)	0.5 mg RBZ (n=125)	Sham/ 0.5 mg RBZ (n=257)	0.3 mg RBZ (n=250)	0.5 mg RBZ (n=252)
Month 24									
Mean (SD)	–126 (198)	–260 (169)	–271 (202)	–133 (209)	–251 (212)	–253 (184)	–130 (203)	–255 (192)	–262 (193)
95% CI for mean [a]	(–160, –91)	(–290, –230)	(–306, –235)	(–170, –97)	(–288, –213)	(–286, –221)	(–155, –105)	(–279, –231)	(–286, –238)
Difference in LS means (vs. sham) [b]		–112	–132		–108	–119		–110	–128
95% CI for difference [b]		(–152, –72)	(–170, –95)		(–149, –67)	(–160, –79)		(–138, –81)	(–155, –100)
P-value (vs. sham)		< 0.0001	< 0.0001		< 0.0001	< 0.0001		< 0.0001	< 0.0001
Month 36									
Mean (SD)	–213 (194)	–262 (181)	–267 (208)	–200 (216)	–261 (197)	–269 (179)	–207 (204)	–262 (188)	–268 (194)
95% CI for mean [a]	(–247, –180)	(–294, –230)	(–303, –230)	(–238, –162)	(–296, –226)	(–301, –237)	(–232, –182)	(–285, –238)	(–292, –244)
Difference in LS means (vs. sham) [b]		–20.3	–38.8		–53.0	–69.2		–37.8	–55.3
95% CI for difference [b]		(–56,15.2)	(–71, –7.0)		(–94, –12)	(–109, –29)		(–65, –11)	(–81, –30)
P-value (vs. sham)		0.2611	0.0171		0.0116	0.0008		0.0061	< 0.0001

RBZ =ranibizumab.

Notes: The last observation carried forward (LOCF) method was used to impute missing data.

Strata were defined using baseline BCVA score (≤ 55, > 55 letters), baseline HbA_{1c} level (≤ 8%, > 8%), prior therapy for DME and baseline CFT in the study eye (yes, no).

[a] Based on the t-distribution.

[b] Based on pairwise ANOVA models adjusted for the baseline strata.

Table 4.6 Mean Number of Macular Laser Treatments at 24 Months and 36 Months

	RIDE			RISE			Pooled		
	Sham/ 0.5 mg RBZ (n=130)	0.3 mg RBZ (n=125)	0.5 mg RBZ (n=127)	Sham/ 0.5 mg RBZ (n=127)	0.3 mg RBZ (n=125)	0.5 mg RBZ (n=125)	Sham/ 0.5 mg RBZ (n=257)	0.3 mg RBZ (n=250)	0.5 mg RBZ (n=252)
Month 24									
Mean (SD)	1.6 (1.6)	0.7 (1.4)	0.3 (0.7)	1.8 (1.8)	0.8 (1.2)	0.8 (1.3)	1.7 (1.7)	0.7 (1.3)	0.5 (1.1)
95% CI for mean [a]	(1.4, 1.9)	(0.5, 1.0)	(0.2, 0.4)	(1.5, 2.1)	(0.5, 1.0)	(0.5, 1.0)	(1.5, 1.9)	(0.6, 0.9)	(0.4, 0.7)
Difference in LS means (vs. sham) [b]		–0.9	–1.3		–1.0	–1.1		–1.0	–1.2
95% CI for difference [b]		(–1.3, –0.5)	(–1.6, –1.0)		(–1.4, –0.7)	(–1.5, –0.7)		(–1.2, –0.7)	(–1.4, –1.0)
P-value (vs. sham)		< 0.0001	< 0.0001		< 0.0001	< 0.0001		< 0.0001	< 0.0001
Month 36									
Mean (SD)	1.7 (1.6)	0.9 (1.8)	0.4 (0.9)	1.9 (1.8)	0.8 (1.4)	0.9 (1.5)	1.8 (1.7)	0.9 (1.6)	0.6 (1.2)
95% CI for mean [a]	(1.5, 2.0)	(0.6, 1.2)	(0.2, 0.5)	(1.5, 2.2)	(0.6, 1.1)	(0.6, 1.1)	(1.6, 2.0)	(0.7, 1.1)	(0.5, 0.8)
Difference in LS means (vs. sham) [b]		–0.8	–1.4		–1.0	–1.0		–0.9	–1.2
95% CI for difference [b]		(–1.3, –0.4)	(–1.7, –1.1)		(–1.4, –0.6)	(–1.4, –0.6)		(–1.2, –0.6)	(–1.5, –0.9)
P-value (vs. sham)		< 0.0001	< 0.0001		< 0.0001	< 0.0001		< 0.0001	< 0.0001

RBZ =ranibizumab.

Notes: Strata were defined using baseline BCVA score (≤ 55, > 55 letters), baseline HbA_{1c} level (≤ 8%, > 8%), and prior therapy for DME in the study eye (yes, no).

[a] Based on the t-distribution.

[b] Based on pairwise ANOVA models adjusted for the baseline strata.

Table 4.7 Proportion of Patients Who Received at Least One Macular Laser Treatment by Month 24 and Month 36

	RIDE			RISE			Pooled		
	Sham/ 0.5 mg RBZ (n =130)	0.3 mg RBZ (n =125)	0.5 mg RBZ (n =127)	Sham/ 0.5 mg RBZ (n =127)	0.3 mg RBZ (n =125)	0.5 mg RBZ (n = 125)	Sham/ 0.5 mg RBZ (n = 257)	0.3 mg RBZ (n = 250)	0.5 mg RBZ (n = 252)
Month 24									
n (%)	91 (70.0%)	45 (36.0%)	25 (19.7%)	94 (74.0%)	49 (39.2%)	44 (35.2%)	185 (72.0%)	94 (37.6%)	69 (27.4%)
95% CI for percentage a	(62.1%, 77.9%)	(27.6%, 44.4%)	(12.8%, 26.6%)	(66.4%, 81.6%)	(30.6%, 47.8%)	(26.8%, 43.6%)	(66.5%, 77.5%)	(31.6%, 43.6%)	(21.9%, 32.9%)
Difference in % (vs. sham) [b]		–32.8%	–49.8%		–35.0%	–39.3%		–34.4%	–44.6%
95% CI for difference [b]		(–44%, –21%)	(–60%, –40%)		(–46%, –24%)	(–51%, –28%)		(–43%, –26%)	(–52%, –37%)
P-value (vs. sham)		< 0.0001	< 0.0001		< 0.0001	< 0.0001		< 0.0001	< 0.0001
Month 36									
n (%)	94 (72.3%)	46 (36.8%)	27 (21.3%)	94 (74.0%)	51 (40.8%)	47 (37.6%)	188 (73.2%)	97 (38.8%)	74 (29.4%)
95% CI for percentage [a]	(64.6%, 80.0%)	(28.3%, 45.3%)	(14.1%, 28.4%)	(66.4%, 81.6%)	(32.2%, 49.4%)	(29.1%, 46.1%)	(67.7%, 78.6%)	(32.8%, 44.8%)	(23.7%, 35.0%)
Difference in % (vs. sham) [b]		–34.4%	–50.7%		–33.6%	–36.5%		–34.4%	–43.8%
95% CI for difference [b]		(–46%, –23%)	(–61%, –40%)		(–45%, –22%)	(–48%, –25%)		(–43%, –26%)	(–52%, –36%)
P-value (vs. sham)		< 0.0001	< 0.0001		< 0.0001	< 0.0001		< 0.0001	< 0.0001

RBZ =ranibizumab. Strata were defined using baseline BCVA score (≤ 55, > 55 letters), baseline HbA_{1c} level (≤ 8%, > 8%), and prior therapy for DME in the study eye (yes, no).
[a] By normal approximation of the observed proportions. [b] Weighted estimates adjusted for the baseline strata using Cochran–Mantel–Haenszel weights and normal approximation of the weighted estimates.

Table 4.8 Proportion of Patients Who Received at Least One Panretinal Photocoagulation Treatment in the Study Eye by Month 24 and Month 36

	RIDE			RISE			Pooled		
	Sham/ 0.5 mg RBZ (n =130)	0.3 mg RBZ (n =125)	0.5 mg RBZ (n =127)	Sham/ 0.5 mg RBZ (n =127)	0.3 mg RBZ (n =125)	0.5 mg RBZ (n = 125)	Sham/ 0.5 mg RBZ (n = 257)	0.3 mg RBZ (n = 250)	0.5 mg RBZ (n = 252)
Month 24									
n (%)	16 (12.3%)	2 (1.6%)	2 (1.6%)	14 (11.0%)	0 (0.0%)	1 (0.8%)	30 (11.7%)	2 (0.8%)	3 (1.2%)
95% CI for percentage [a]	(6.7%, 18.0%)	(0.0%, 3.8%)	(0.0%, 3.7%)	(5.6%, 16.5%)	(0.0%, 0.0%)	(0.0%, 2.4%)	(7.7%, 15.6%)	(0.0%, 1.9%)	(0.0%, 2.5%)
Difference in % (vs. sham) [b]		−10.8%	−10.9%		−11.0%	−10.1%		−10.9%	−10.3%
95% CI for difference [b]		(−17%, −4.9%)	(−17%, −5.0%)		(−16%, −5.8%)	(−15%, −4.7%)		(−15%, −6.9%)	(−14%, −6.3%)
P-values		<0.0001	<0.0001		<0.0001	<0.0001		<0.0001	<0.0001
Month 36									
n (%)	18 (13.8%)	4 (3.2%)	3 (2.4%)	16 (12.6%)	0 (0.0%)	3 (2.4%)	34 (13.2%)	4 (1.6%)	6 (2.4%)
95% CI for percentage [a]	(7.9%, 19.8%)	(0.1%, 6.3%)	(0.0%, 5.0%)	(6.8%, 18.4%)	(0.0%, 0.0%)	(0.0%, 5.1%)	(9.1%, 17.4%)	(0.0%, 3.2%)	(0.5%, 4.3%)
Difference in % (vs. sham) [b]		−10.5%	−11.5%		−13.0%	−10.2%		−11.8%	−10.8%
95% CI for difference [b]		(−17%, −4.0%)	(−18%, −5.2%)		(−19%, −7.2%)	(−17%, −3.8%)		(−16%, −7.4%)	(−15%, −6.4%)
P-values		0.0036	0.0009		<0.0001	0.0029		<0.0001	<0.0001

RBZ =ranibizumab.

Notes: Strata were defined using baseline BCVA score (≤ 55, > 55 letters), baseline HbA_{1c} level (≤ 8%, > 8%), and prior therapy for DME in the study eye (yes, no).

[a] By normal approximation of the observed proportions.

[b] Weighted estimates adjusted for the baseline strata using Cochran–Mantel–Haenszel weights and normal approximation of the weighted estimates.

Table 4.9 Proportion of Patients with ≥ 3-Step Progression from Baseline and ≥ 2-Step Progression from Baseline in ETDRS Diabetic Retinopathy Severity Level in the Study Eye at 24 and 36 Months

	Progression of ≥3 Steps from Baseline			Progression of ≥2 Steps from Baseline		
	Sham/ 0.5 mg RBZ (n=257)	0.3 mg RBZ (n=250)	0.5 mg RBZ (n=252)	Sham/ 0.5 mg RBZ (n=257)	0.3 mg RBZ (n=250)	0.5 mg RBZ (n=252)
Month 24						
n (%)	12 (5.0%)	3 (1.3%)	2 (0.9%)	23 (9.6%)	4 (1.7%)	5 (2.1%)
95% CI for percentage [a]	(2.3%, 7.8%)	(0.0%, 2.7%)	(0.0%, 2.0%)	(5.9%, 13.4%)	(0.0%, 3.4%)	(0.3%, 4.0%)
Difference in % (vs. sham) [b]		–3.5%	–4.2%		–7.7%	–7.6%
95% CI for difference [b]		(–6.6%, –0.3%)	(–7.2%, –1.2%)		(–12%, –3.6%)	(–12%, –3.4%)
P-value vs. sham		0.0355	0.0072		0.0004	0.0005
Month 36						
n (%)	9 (3.8%)	3 (1.3%)	3 (1.3%)	22 (9.2%)	6 (2.6%)	7 (3.0%)
95% CI for percentage [a]	(1.4%, 6.2%)	(0.0%, 2.7%)	(0.0%, 2.7%)	(5.5%, 12.9%)	(0.5%, 4.6%)	(0.8%, 5.2%)
Difference in % (vs. sham) [b]		–2.3%	–2.5%		–6.6%	–6.3%
95% CI for difference [b]		(–5.0%, 0.4%)	(–5.3%, 0.3%)		(–11%, –2.3%)	(–11%, –2.1%)
P-value vs. sham		0.1219	0.0844		0.0030	0.0044

ETDRS =Early Treatment of Diabetic Retinopathy Study; RBZ =ranibizumab.

Notes: The last observation carried forward (LOCF) method was used to impute missing data.

Strata were defined using baseline BCVA score (≤ 55, > 55 letters), baseline HbA_{1c} level (≤ 8%, > 8%), and prior therapy for DME in the study eye (yes, no).

[a] By normal approximation of the observed proportions.

[b] Weighted estimates adjusted for the baseline strata using Cochran–Mantel–Haenszel weights and normal approximation of the weighted estimates.

Appendix 5 NEI VFQ-25 Composite and Subscale Scores at Month 24

Table 5.1 Mean Change from Baseline in the NEI VFQ-25 Composite and Subscale Scores at Month 24

Change in NEI VFQ-25 Subscale Score at Month 24	RIDE			RISE		
	Sham (n = 130)	0.3 mg Ranibizumab (n = 125)	0.5 mg Ranibizumab (n = 127)	Sham (n = 127)	0.3 mg Ranibizumab (n = 125)	0.5 mg Ranibizumab (n = 125)
Overall visual function, NEI VFQ-25 composite						
Mean (SD)	4.0 (17.6)	7.3 (16.2)	6.9 (14.2)	4.4 (16.3)	7.0 (14.9)	7.5 (15.7)
95% CI for mean [a]	(0.9, 7.0)	(4.4, 10.2)	(4.5, 9.4)	(1.5, 7.3)	(4.4, 9.7)	(4.7, 10.3)
Difference in LS means (vs.		2.1	2.7		4.6	3.8
95% CI for difference [b]		(–1.9, 6.0)	(–0.9, 6.4)		(1.1, 8.1)	(0.3, 7.4)
p-value (vs. sham) [b]		0.3002	0.1441		0.0101	0.0342
Near activities						
Mean (SD)	9.0 (23.7)	10.9 (21.3)	10.9 (19.8)	6.1 (20.6)	11.5 (21.9)	12.4 (19.5)
95% CI for mean [a]	(4.8, 13.1)	(7.1, 14.7)	(7.4, 14.3)	(2.4, 9.7)	(7.6, 15.4)	(8.9, 15.8)
Distance activities						
Mean (SD)	3.6 (19.9)	7.5 (20.2)	7.6 (17.6)	2.7 (20.4)	8.0 (20.6)	6.2 (22.5)
95% CI for mean [a]	(0.1, 7.1)	(3.9, 11.0)	(4.5, 10.7)	(–1.0, 6.3)	(4.3, 11.6)	(2.2, 10.2)
Vision-specific dependency						
Mean (SD)	1.2 (31.5)	8.9 (27.7)	8.0 (25.8)	5.6 (28.6)	6.5 (24.7)	6.3 (29.1)
95% CI for mean [a]	(–4.3, 6.7)	(4.0, 13.8)	(3.5, 12.5)	(0.5, 10.7)	(2.2, 10.9)	(1.1, 11.5)
Driving						
Mean (SD)	–2.2 (26.6)	2.6 (22.4)	5.5 (21.8)	1.0 (25.6)	1.8 (25.0)	5.7 (25.8)
95% CI for mean [a]	(–7.4, 2.9)	(–1.7, 6.8)	(1.4, 9.6)	(–3.7, 5.8)	(–2.9, 6.5)	(0.8, 10.6)

Note: The LOCF method was used to impute missing data.

[a] Derived from the t-distributions.

[b] Based on pairwise analysis of covariance models adjusted for baseline visual acuity (≤ 55, > 55 letters); baseline HbA_{1c} (≤ 8%, >8%); and prior therapy for DME (yes, no), and baseline value of the corresponding endpoint.

Table 5.1 Mean Change from Baseline in the NEI VFQ-25 Composite and Subscale Scores at Month 24 (cont.)

Change in NEI VFQ-25 Subscale Score at Month 24	RIDE			RISE		
	Sham (n = 130)	0.3 mg Ranibizumab (n = 125)	0.5 mg Ranibizumab (n = 127)	Sham (n = 127)	0.3 mg Ranibizumab (n = 125)	0.5 mg Ranibizumab (n = 125)
General Health						
Mean (SD)	–1.0 (22.3)	2.2 (19.1)	4.1 (20.1)	4.2 (21.0)	1.6 (21.6)	–1.8 (21.7)
95% CI for mean [a]	(–4.9, 2.9)	(–1.2, 5.6)	(0.6, 7.7)	(0.5, 7.9)	(–2.2, 5.4)	(-5.7, 2.0)
Vision-specific role difficulties						
Mean (SD)	7.9 (29.0)	12.0 (28.6)	9.4 (25.2)	4.8 (26.5)	9.1 (26.4)	7.5 (27.6)
95% CI for mean [a]	(2.8, 13.0)	(7.1, 17.3)	(5.0, 13.9)	(0.1, 9.5)	(4.4, 13.8)	(2.6, 12.4)
Vision-specific mental health						
Mean (SD)	5.4 (26.9)	14.6 (26.0)	12.5 (22.4)	9.1 (26.1)	11.4 (24.4)	14.8 (24.0)
95% CI for mean [a]	(0.7, 10.1)	(9.9, 19.2)	(8.6, 16.5)	(4.4, 13.7)	(7.1, 15.7)	(10.6, 19.1)
General Vision						
Mean (SD)	7.3 (18.4)	8.5 (16.9)	9.8 (16.9)	9.1 (17.9)	9.8 (15.2)	11.5 (18.8)
95% CI for mean [a]	(4.1, 10.6)	(5.5, 11.5)	(6.8, 12.7)	(6.0, 12.3)	(7.1, 12.5)	(8.1, 14.8)
Vision-specific social functioning						
Mean (SD)	0.8 (21.9)	4.8 (24.8)	3.2 (19.1)	1.5 (23.8)	3.9 (20.9)	2.5 (22.7)
95% CI for mean [a]	(–3.1, 4.6)	(0.4, 9.2)	(–0.1, 6.6)	(–2.7, 5.7)	(0.2, 7.6)	(–1.5, 6.6)
Color Vision						
Mean (SD)	0.8 (24.9)	2.4 (20.8)	1.8 (22.2)	2.2 (26.3)	3.0 (22.4)	2.2 (21.1)
95% CI for mean [a]	(–3.6, 5.2)	(–1.3, 6.1)	(–2.1, 5.7)	(–2.5, 6.9)	(–1.0, 7.0)	(–1.5, 6.0)

Note: The LOCF method was used to impute missing data.

[a] Derived from the t-distributions.

[b] Based on pairwise analysis of covariance models adjusted for baseline visual acuity (≤ 55, > 55 letters); baseline HbA_{1c} (≤ 8%, >8%); and prior therapy for DME (yes, no), and baseline value of the corresponding endpoint.

Table 5.1 Mean Change from Baseline in the NEI VFQ-25 Composite and Subscale Scores at Month 24 (cont.)

Change in NEI VFQ-25 Subscale Score at Month 24	RIDE			RISE		
	Sham (n = 130)	0.3 mg Ranibizumab (n = 125)	0.5 mg Ranibizumab (n = 127)	Sham (n = 127)	0.3 mg Ranibizumab (n = 125)	0.5 mg Ranibizumab (n = 125)
Peripheral Vision						
Mean (SD)	4.6 (27.1)	4.2 (26.4)	3.9 (24.1)	2.8 (22.9)	4.6 (25.8)	6.7 (23.8)
95% CI for mean [a]	(–0.2, 9.3)	(–0.5, 8.9)	(–0.3, 8.2)	(–1.3, 6.9)	(0.1, 9.2)	(2.5, 10.9)
Ocular Pain						
Mean (SD)	2.6 (19.1)	1.7 (20.3)	3.5 (20.0)	3.8 (18.4)	5.2 (17.2)	5.9 (18.8)
95% CI for mean [a]	(–0.7, 6.0)	(–1.9, 5.3)	(0.0, 7.1)	(0.5, 7.1)	(2.2, 8.2)	(2.6, 9.3)

Note: The LOCF method was used to impute missing data.

[a] Derived from the t-distributions.

[b] Based on pairwise analysis of covariance models adjusted for baseline visual acuity (≤ 55, > 55 letters); baseline HbA_{1c} (≤ 8%, >8%); and prior therapy for DME (yes, no), and baseline value of the corresponding endpoint.

Appendix 6 36-Month Safety Results

Table 6.1 Common Ocular Adverse Events in the Study Eye Occurring at a Rate of ≥5% in Either Ranibizumab Group at Month 36

MedDRA Preferred Term	Sham Month 0-24 (n=250)	Sham/ 0.5 mg [a] Month 0-36 (n=251)	0.3 mg RBZ Month 0-36 (n=250)	0.5 mg RBZ Month 0-36 (n=249)
Conjunctival hemorrhage	79 (31.6%)	90 (35.9%)	124 (49.6%)	129 (51.8%)
Cataract	48 (19.2%)	59 (23.5%)	58 (23.2%)	58 (23.3%)
Macular edema	52 (20.8%)	60 (23.9%)	57 (22.8%)	54 (21.7%)
Retinal hemorrhage	49 (19.6%)	52 (20.7%)	39 (15.6%)	54 (21.7%)
Retinal exudates	39 (15.6%)	47 (18.7%)	50 (20.0%)	44 (17.7%)
Eye pain	32 (12.8%)	39 (15.5%)	49 (19.6%)	48 (19.3%)
Vitreous detachment	38 (15.2%)	42 (16.7%)	35 (14.0%)	42 (16.9%)
Intraocular pressure increased	17 (6.8%)	25 (10.0%)	46 (18.4%)	46 (18.5%)
Vitreous floaters	11 (4.4%)	16 (6.4%)	32 (12.8%)	33 (13.3%)
Ocular hyperemia	23 (9.2%)	24 (9.6%)	25 (10.0%)	19 (7.6%)
Eye irritation	12 (4.8%)	15 (6.0%)	21 (8.4%)	19 (7.6%)
Cataract cortical	20 (8.0%)	16 (6.4%)	17 (6.8%)	13 (5.2%)
Foreign body sensation in eyes	12 (4.8%)	14 (5.6%)	27 (10.8%)	12 (4.8%)
Vision blurred	11 (4.4%)	12 (4.8%)	25 (10.0%)	16 (6.4%)
Dry eye	8 (3.2%)	16 (6.4%)	20 (8.0%)	19 (7.6%)
Macular fibrosis	0	23 (9.2%)	15 (6.0%)	24 (9.6%)
Diabetic retinal edema	15 (6.0%)	15 (6.0%)	17 (6.8%)	14 (5.6%)
Lacrimation increased	10 (4.0%)	14 (5.6%)	15 (6.0%)	20 (8.0%)
Visual acuity reduced	15 (6.0%)	16 (6.4%)	13 (5.2%)	11 (4.4%)
Cataract nuclear	13 (5.2%)	12 (4.8%)	12 (4.8%)	14 (5.6%)
Cataract subcapsular	13 (5.2%)	10 (4.0%)	14 (5.6%)	14 (5.6%)
Retinal aneurysm	6 (2.4%)	7 (2.8%)	14 (5.6%)	6 (2.4%)

RBZ=ranibizumab. Counts represent number of patients reporting the event. There is no pure sham control group at Month 36 so it is not valid to compare the sham groups with the ranibizumab treatment arms.

[a] Patients initially randomized to sham including those who crossed over to 0.5 mg ranibizumab during Year 3.

Table 6.2 Ocular Serious Adverse Events in the Study Eye Occurring in ≥ 2 Patients in Any Treatment Group during the 36-Month Treatment Period

MedDRA Preferred Term	Sham Month 0-24 (n=250)	Sham/ 0.5 mg [a] Month 0-36 (n=251)	0.3 mg RBZ Month 0-36 (n=250)	0.5 mg RBZ Month 0-36 (n=249)
Cataract	0	1 (0.4%)	1 (0.4%)	3 (1.2%)
Visual acuity reduced	4 (1.6%)	3 (1.2%)	0	3 (1.2%)
Vitreous hemorrhage	7 (2.8%)	9 (3.6%)	1 (0.4%)	3 (1.2%)
Cataract traumatic	0	0	2 (0.8%)	2 (0.8%)
Endophthalmitis	0	0	4 (1.6%)	2 (0.8%)
Intraocular pressure increased	0	0	0	2 (0.8%)
Medication error	0	0	2 (0.8%)	2 (0.8%)
Diabetic retinal edema	0	0	2 (0.8%)	1 (0.4%)
Macular edema	2 (0.8%)	1 (0.4%)	0	1 (0.4%)
Retinal detachment	1 (0.4%)	2 (0.8%)	0	1 (0.4%)

RBZ=ranibizumab. Counts represent number of patients reporting the event. There is no pure sham control group at Month 36 so it is not valid to compare the sham groups with the ranibizumab treatment arms.

[a] Patients initially randomized to sham including those who crossed over to 0.5 mg ranibizumab during Year 3.

Table 6.3 Per-injection Rates of Selected Ocular Serious Adverse Events in the Study Eye during the 36-Month Treatment Period

MedDRA Preferred Term	Sham Month 0-24 (n=250)	Sham/ 0.5 mg [a] Month 0-36 (n=251)	0.3 mg RBZ Month 0-36 (n=250)	0.5 mg RBZ Month 0-36 (n=249)
Total Number of Injections	5108	7056	7223	7327
Cataract traumatic	0	0	2 (0.0277%)	2 (0.0273%)
Endophthalmitis	0	0	4 (0.0554%)	2 (0.0273%)
Intraocular inflammation	0	0	0	0
Presumed endophthalmitis	0	0	0	0
Retinal detachment	1 (0.0196%)	2 (0.0283%)	0	2 (0.0273%)
Retinal tear	0	0	0	1 (0.0136%)

RBZ=ranibizumab. Counts represent number of patients reporting the event. There is no pure sham control group at Month 36 so it is not valid to compare the sham groups with the ranibizumab treatment arms.

[a] Patients initially randomized to sham including those who crossed over 0.5 mg ranibizumab during Year 3.

Table 6.4 Ocular Adverse Events in the Study Eye Leading to Treatment Discontinuation in ≥2 Patients in Any Treatment Group during the 36-Month Treatment Period

MedDRA Preferred Term	Sham Month 0-24 (n=250)	Sham/ 0.5 mg [a] Month 0-36 (n=251)	0.3 mg RBZ Month 0-36 (n=250)	0.5 mg RBZ Month 0-36 (n=249)
Diabetic retinal edema	2 (0.8%)	2 (0.8%)	0	1 (0.4%)
Endophthalmitis	0	0	2 (0.8%)	1 (0.4%)
Diabetic retinopathy	2 (0.8%)	2 (0.8%)	0	0
Macular edema	2 (0.8%)	2 (0.8%)	0	0
Vitreous hemorrhage	4 (1.6%)	4 (1.6%)	0	0

RBZ=ranibizumab. Counts represent number of patients reporting the event. There is no pure sham control group at Month 36 so it is not valid to compare the sham groups with the ranibizumab treatment arms.

[a] Patients initially randomized to sham including those who crossed over to 0.5 mg ranibizumab during Year 3.

Table 6.5 Common (≥ 5%) Non-Ocular Adverse Events with ≥ 2% Higher Frequency in the 0.5 mg Ranibizumab Group than the 0.3 mg Ranibizumab Group during the 36-Month Study Period

MedDRA Preferred Term	Sham Month 0-24 (n=250)	Sham/ 0.5 mg [a] Month 0-36 (n=251	0.3 mg RBZ Month 0-36 (n=250)	0.5 mg RBZ Month 0-36 (n=249)
Hypertension	48 (19.2%)	57 (22.7%)	56 (22.4%)	63 (25.3%)
Anemia	25 (10.0%)	30 (12.0%)	34 (13.6%)	42 (16.9%)
Urinary tract infection	28 (11.2%)	35 (13.9%)	19 (7.6%)	31 (12.4%)
Cardiac failure congestive	12 (4.8%)	20 (8.0%)	16 (6.4%)	26 (10.4%)
Diarrhea	11 (4.4%)	13 (5.2%)	16 (6.4%)	26 (10.4%)
Pneumonia	16 (6.4%)	20 (8.0%)	19 (7.6%)	25 (10.0%)
Bronchitis	11 (4.4%)	16 (6.4%)	18 (7.2%)	23 (9.2%)
Sinusitis	20 (8.0%)	25 (10.0%)	15 (6.0%)	21 (8.4%)
Back pain	18 (7.2%)	25 (10.0%)	11 (4.4%)	16 (6.4%)
Dizziness	13 (5.2%)	16 (6.4%)	9 (3.6%)	14 (5.6%)

RBZ=ranibizumab. Counts represent number of patients reporting the event. There is no pure sham control group at Month 36 so it is not valid to compare the sham groups with the ranibizumab treatment arms.

[a] Patients initially randomized to sham including those who crossed over to 0.5 mg ranibizumab during Year 3.

Table 6.6 Non-Ocular Serious Adverse Events with ≥ 1% Higher Frequency in the 0.5 mg Ranibizumab Group than the 0.3 mg Ranibizumab Group during the 36-Month Study Period

MedDRA Preferred Term	Sham Month 0-24 (n=250)	Sham/ 0.5 mg [a] Month 0-36 (n=251	0.3 mg RBZ Month 0-36 (n=250)	0.5 mg RBZ Month 0-36 (n=249)
Pneumonia	7 (2.8%)	8 (3.2%)	7 (2.8%)	13 (5.2%)
Cerebrovascular accident	3 (1.2%)	3 (1.2%)	4 (1.6%)	9 (3.6%)
Hypertension	1 (0.4%)	(0.0%)	4 (1.6%)	8 (3.2%)
Anemia	2 (0.8%)	2 (0.8%)	3 (1.2%)	6 (2.4%)
Colon cancer	0	0	0	3 (1.2%)
Gastroenteritis	0	0	0	3 (1.2%)
Infected skin ulcer	0	0	0	3 (1.2%)
Pancreatitis acute	0	0	0	3 (1.2%)
Presyncope	1 (0.4%)	1 (0.4%)	0	3 (1.2%)

RBZ=ranibizumab. Counts represent number of patients reporting the event. There is no pure sham control group at Month 36 so it is not valid to compare the sham groups with the ranibizumab treatment arms.

[a] Patients initially randomized to sham including those who crossed over to 0.5 mg ranibizumab during Year 3.

Table 6.7 Non-Ocular Adverse Events Leading to Treatment Discontinuation in ≥2 Patients in Any Treatment Group during the 36-Month Treatment Period

MedDRA Preferred Term	Sham Month 0-24 (n=250)	Sham/ 0.5 mg [a] Month 0-36 (n=251	0.3 mg RBZ Month 0-36 (n=250)	0.5 mg RBZ Month 0-36 (n=249)
Cerebrovascular accident	1 (0.4%)	1 (0.4%)	2 (0.8%)	3 (1.2%)
Cardiac arrest	1 (0.4%)	1 (0.4%)	1 (0.4%)	2 (0.8%)
Myocardial infarction	1 (0.4%)	2 (0.8%)	0	1 (0.4%)
Pneumonia	0	0	2 (0.8%)	1 (0.4%)
Renal failure	2 (0.8%)	2 (0.8%)	0	1 (0.4%)
Acute myocardial infarction	0	1 (0.4%)	2 (0.8%)	0
Respiratory failure	0	0	2 (0.8%)	0

RBZ=ranibizumab. Counts represent number of patients reporting the event. There is no pure sham control group at Month 36 so it is not valid to compare the sham groups with the ranibizumab treatment arms.

[a] Patients initially randomized to sham including those who crossed over to 0.5 mg ranibizumab during Year 3.

Table 6.8 Non-Ocular Adverse Events of Special Interest during the 36-Month Treatment Period

AE Group Term	Sham Month 0-24 (n=250)	Sham/ 0.5 mg [a] Month 0-36 (n=251	0.3 mg RBZ Month 0-36 (n=250)	0.5 mg RBZ Month 0-36 (n=249)
Any non-ocular AESI	89 (35.6%)	106 (42.2%)	109 (43.6%)	112 (45.0%)
Any bleeding/hemorrhage adverse event	12 (4.8%)	17 (6.8%)	20 (8.0%)	26 (10.4%)
Bleeding/hemorrhage (CNS and cerebrovascular hemorrhage)	3 (1.2%)	5 (2.0%)	5 (2.0%)	9 (3.6%)
Bleeding/hemorrhage (non-CNS hemorrhage)	9 (3.6%)	12 (4.8%)	16 (6.4%)	19 (7.6%)
Congestive heart failure	15 (6.0%)	23 (9.2%)	19 (7.6%)	27 (10.8%)
Fistulae (other)	0	0	5 (2.0%)	0
Gastrointestinal perforation	0	1 (0.4%)	1 (0.4%)	1 (0.4%)
Hypertension	51 (20.4%)	60 (23.9%)	62 (24.8%)	71 (28.5%)
Proteinuria	11 (4.4%)	10 (4.0%)	12 (4.8%)	9 (3.6%)
Thromboembolic event, arterial	20 (8.0%)	25 (10.0%)	30 (12.0%)	29 (11.6%)
Thromboembolic event, venous	1 (0.4%)	2 (0.8%)	6 (2.4%)	4 (1.6%)
Wound healing complications	0	0	3 (1.2%)	7 (2.8%)

AESI=adverse events of special interest; RBZ=ranibizumab. Counts represent number of patients reporting the event. There is no pure sham control group at Month 36 so it is not valid to compare the sham groups with the ranibizumab treatment arms.

[a] Patients initially randomized to sham including those who crossed over to 0.5 mg ranibizumab during Year 3.

Table 6.9 Non-Ocular Serious Adverse Events of Special Interest during the 36-Month Treatment Period

AE Group Term	Sham Month 0-24 (n=250)	Sham/ 0.5 mg [a] Month 0-36 (n=251	0.3 mg RBZ Month 0-36 (n=250)	0.5 mg RBZ Month 0-36 (n=249)
Any non-ocular serious AESI	29 (11.6%)	33 (13.1%)	42 (16.8%)	49 (19.7%)
Any bleeding/hemorrhage adverse event	7 (2.8%)	8 (3.2%)	11 (4.4%)	13 (5.2%)
Bleeding/hemorrhage (CNS and cerebrovascular hemorrhage)	3 (1.2%)	3 (1.2%)	5 (2.0%)	9 (3.6%)
Bleeding/hemorrhage (non-CNS hemorrhage)	4 (1.6%)	5 (2.0%)	6 (2.4%)	5 (2.0%)
Congestive heart failure	11 (4.4%)	13 (5.2%)	10 (4.0%)	14 (5.6%)
Fistulae (other)	0	0	2 (0.8%)	0
Gastrointestinal perforation	0	0	0	1 (0.4%)
Hypertension	1 (0.4%)	1 (0.4%)	4 (1.6%)	10 (4.0%)
Proteinuria	0	0	0	1 (0.4%)
Thromboembolic event, arterial	17 (6.8%)	21 (8.4%)	26 (10.4%)	26 (10.4%)
Thromboembolic event, venous	1 (0.4%)	1 (0.4%)	4 (1.6%)	3 (1.2%)
Wound healing complications	0	0	0	1 (0.4%)

RBZ=ranibizumab. Counts represent number of patients reporting the event. There is no pure sham control group at Month 36 so it is not valid to compare the sham groups with the ranibizumab treatment arms.

[a] Patients initially randomized to sham including those who crossed over to 0.5 mg ranibizumab during Year 3.

Table 6.10 Causes of Death by Treatment Group

Treatment Group	Age (yr)	Sex	Race	Death of Date	Study Day of Death	No. of Prior Treatments with Study Drug	Days Since Last Treatment with Study Drug	SAE Resulting in Death	Autopsy Performed
Sham/ 0.5 mg	73	F	White	(b) (6)	735	24	33	Cardiopulmonary arrest	Unknown
	75	F	White		–	25	30	Myocardial infarction	No
	59	F	White		368	8	139	Myocardial infarction	Unknown
	57	M	Not Available		534	17	24	Myocardial infarction	No
	61	M	White		1072	34	18	Gas gangrene	No
	80	M	White		587	19	19	Cardiac arrest	No
	80	M	White		587	19	19	Renal failure	Unknown
	62	M	White		841	24	50	Ischemic cardiomyopathy	No
0.3 mg	60	M	White		503	16	55	Respiratory failure	Unknown
	60	M	White		–	16	55	Congestive heart failure	No
	83	M	White		548	18	37	Aortic aneurysm rupture	Unknown
	78	M	White		830	24	52	Acute heart failure	Unknown
	70	F	Black or African American		425	8	35	Cardiac arrest	Unknown

Table 6.10 Causes of Death by Treatment Group (cont.)

Treatment Group	Age (yr)	Sex	Race	Death of Date	Study Day of Death	No. of Prior Treatments with Study Drug	Days Since Last Treatment with Study Drug	SAE Resulting in Death	Autopsy Performed
0.3 mg (cont.)	83	F	White	(b) (6)	722	21	28	Cerebrovascular accident	No
	79	F	White		978	33	11	Death	Unknown
	59	M	White		770	26	18	Hypertension worsened	No
	59	M	White		770	26	18	Atherosclerotic cardiovascular disease	No
	62	F	White		823	27	10	Coronary artery occlusion	Unknown
	67	M	White		270	7	28	Cardiac arrest	No
	59	F	Black or African American		416	14	23	End stage renal disease (ESRD)	Unknown
	59	F	Black or African American		416	14	23	Respiratory failure	Unknown
	61	M	White		514	15	82	Clostridium difficile infection	Unknown
0.5 mg	59	F	White		985	32	19	Coronary artery disease	Unknown
	59	F	White		985	32	19	Sepsis syndrome	Unknown

Table 6.10 Causes of Death by Treatment Group (cont.)

Treatment Group	Age (yr)	Sex	Race	Death of Date	Study Day of Death	No. of Prior Treatments with Study Drug	Days Since Last Treatment with Study Drug	SAE Resulting in Death	Autopsy Performed
0.5 mg (cont.)	73	M	White	(b) (6)	1064	33	106	Pancreatic cancer metastatic	Unknown
	64	F	White		286	9	19	Coronary artery disease aggravated	Yes
	64	F	White		286	9	19	Cardiac arrest	Unknown
	79	M	White		–	29	36	Pneumonia	Unknown
	79	M	White		940	29	36	Cardiac arrhythmia	No
	77	M	White		490	14	97	Acute renal failure	Unknown
	47	M	White		322	11	27	Carbon monoxide poisoning	Unknown
	56	M	Asian		182	5	62	Congestive heart failure	No
	56	M	Asian		182	5	62	Coronary artery disease	Unknown
	83	F	White		52	2	23	Pneumonia	Unknown
	71	M	White		520	11	137	Cardiac arrest	Yes
	29	M	Black or African American		935	31	29	Cardiopulmonary arrest	No
	52	M	White		629	20	21	Unknown cause of death	Unknown
	76	M	White		141	5	22	Perforated colon	Unknown

Table 6.10 Causes of Death by Treatment Group (cont.)

Treatment Group	Age (yr)	Sex	Race	Death of Date	Study Day of Death	No. of Prior Treatments with Study Drug	Days Since Last Treatment with Study Drug	SAE Resulting in Death	Autopsy Performed
0.5 mg (cont.)	65	M	White	(b) (6)	596	20	28	Coronary artery disease	Unknown
	59	F	White		879	25	24	Sepsis	Unknown
	66	F	White		421	14	26	Ventricular fibrillation	Unknown
	69	F	White		688	14	176	Cerebrovascular accident	Yes

Appendix 7 Cox Regression Analysis Results for Stroke, Deaths, Vascular Deaths, and Myocardial Infarction

Post hoc exploratory analyses were performed using the Cox regression model to investigate potential baseline risk factors for stroke, death, vascular death, and myocardial infarction, and whether the treatment differences in these events could be explained by these risk factors. The following baseline factors were evaluated:

- Baseline characteristics
  - Female and age > 65, male and age > 55 versus others
  - Never smoked versus previous or current smoker
  - White versus Non-White
  - HbA_{1c} level ≤ 8% versus > 8%
- Medical history
  - Hypertension versus others
  - Non-ocular hemorrhage versus others
  - Diverticular disease versus others
  - Endarterectomy versus others
  - Nose bleed versus others
  - Rheumatoid arthritis versus others
  - CVA or TIA versus others
  - Cardiac disease (angina, MI, congestive heart failure, coronary artery bypass graft, stent, coronary artery disease, and arrhythmia) versus others
  - Renal disease (renal failure, proteinuria) versus others
  - Anti-angina versus others
- Baseline concomitant medications
  - Prior use of anticoagulant drugs versus others
  - Prior use of antihypertensive drugs versus others
  - Prior use of anti-arrhythmic drugs versus others
  - Prior use of platelet aggregation inhibitors versus others
  - Prior use of lipid-lowering drugs versus others

Study and dose were retained in all models, and each of the potential risk factors were evaluated in a stepwise fashion using a significance level of 0.10 as the criterion for a term entering or remaining in the model. Interactions between treatment and covariates were also evaluated, but none were found to be statistically significant; this could be attributed to the low number of the events and of some of the risk factors. For Month 36, the sham/0.5-mg group included all patients initially randomized to sham regardless of

whether they crossed over to 0.5 mg ranibizumab during the third year; the sham/0.5-mg group was no longer a pure control group and the conclusions that can be drawn from the for 36-month data are limited. The following table shows the final fitted Cox proportional hazards models following the stepwise selection procedure for death, vascular death, stroke, and MI at Month 24 and 36. Baseline risk factors might be correlated. The models selected the most influential factors for patients in the RIDE and RISE studies.

Table 7.1 Final Cox Regression Models

Event	Months	Baseline Risk Factor	Hazard Ratio	95% CI	p-value
Death	0-24	0.5 mg vs. sham	3.2	0.9–11.6	0.075
		0.3 mg vs. sham	2.1	0.5–8.3	0.278
		History of smoking (yes vs. no)	4.0	1.4–10.9	0.007
		Anticoagulant drug use (yes vs. no)	7.7	2.5–23.6	<0.001
	0-36	0.5 mg vs. sham/0.5 mg	2.2	0.9–5.3	0.088
		0.3 mg vs. sham/0.5 mg	1.8	0.7–4.7	0.230
		Prior cardiac diagnosis: yes vs. no	2.9	1.4–6.0	0.004
		Anti-arrhythmic drugs: yes vs. no	2.9	1.1–7.9	0.038
Vascular Death	0-24	0.5 mg vs. sham	2.5	0.6–10.0	0.196
		0.3 mg vs. sham	1.8	0.4–7.6	0.438
		History of smoking (yes vs. no)	3.9	1.1–14.3	0.037
		Aspirin use (yes vs. no)	4.6	1.3–16.9	0.021
		Anticoagulant drug use (yes vs, no)	10.9	2.9–40.2	<0.001
	0-36	0.5 mg vs. sham/0.5 mg	1.8	0.6–5.4	0.287
		0.3 mg vs. sham/0.5 mg	1.8	0.6–5.5	0.318
		Prior cardiac diagnosis (yes vs. no)	3.7	1.6–9.0	0.003
Stroke	0-24	0.5 mg vs. sham	2.1	0.6–6.8	0.241
		0.3 mg vs. sham	0.7	0.2–3.3	0.682
		Prior CVA/TIA (yes vs. no)	5.2	1.6–17.2	0.007
		Lipid lowering drug use (yes vs. no)	0.3	0.1–0.9	0.038
	0-36	0.5 mg vs. sham/0.5 mg	2.1	0.8–5.5	0.151
		0.3 mg vs. sham/0.5 mg	0.8	0.3–2.7	0.746
		Prior CVA/TIA (yes vs. no)	4.4	1.7–11.2	0.002
MI [a]	0-36	0.5 mg vs. sham/0.5 mg	0.7	0.3–1.5	0.332
		0.3 mg vs. sham/0.5 mg	1.5	0.7–3.1	0.249
		Prior cardiac diagnosis (yes vs. no)	3.2	1.7–6.1	<0.001

CVA = cerebrovascular accident; TIA = transient ischemic attack.

[a] Cox regression analyses for MI at Month 24 were not performed because no imbalance was seen among treatment groups at the time of the Month 24 analysis.

Death from Any Cause

At Month 24, after adjusting for the baseline risk factors, the rate of death remained higher in the 0.5-mg group than in the sham group, with a hazard ratio (HR) of 3.2 (95% CI, 0.9,11.6); the difference between the 0.3-mg and sham groups was less apparent, with an HR of 2.1 (95% CI, 0.5, 8.3). The 36-month results are similar to the 24-month results.

Risk factors identified by the models influencing death included a history of smoking, prior cardiac diagnoses, prior use of anticoagulant drugs, and/or prior use of anti-coagulant drugs. The baseline risk factors for death identified by Month 24 and Month 36 data are different. Additional events occurred between Months 24 and 36, thus the identified risk factors changed. Because of the low number of events, predictive risk factors cannot be reliably identified.

Vascular Death

At Month 24, after adjusting for the baseline risk factors, the HRs for vascular death rates between sham and each of the ranibizumab groups were similar and differences between the ranibizumab arms were less apparent. The 36-month results were similar. Similar to death from any cause, baseline factors associated with higher risk of vascular death cannot be robustly determined from this dataset.

Strokes

The incidence of stroke was similar between 0.3-mg and sham groups at both Month 24 and Month36. Stroke rates were higher in the 0.5-mg groups. After adjusting for risk factors, the stroke rates remained higher in the 0.5-mg group compared with the sham groups at both Months 24 and 36. Similar to death from any cause, baseline factors associated with higher risk of stroke events cannot be robustly determined from this dataset. The history of cerebrovascular accidents (CVA) and/or transient ischemic attack (TIA) was found to be associated with stroke at both Months 24 and 36. Patients using lipid-lowering agents at baseline were found to have a reduced risk of stroke at Month 24, but this factor was no longer associated with the stroke rate at Month 36.

Myocardial Infarction

Myocardial Infarction was only modeled at Month 36 because there was no imbalance in rates at Month 24. At Month 36, MIs occurred in 18 (7.2%) patients in the 0.3-mg group, 9 (3.6%) patients in the 0.5-mg group, and 13 (5.2%) patients in the sham/0.5-mg groups (3 MIs occurred during the third year). After adjusting for prior cardiac diagnoses, the MI rate in the 0.3-mg group still trended higher than the sham/0.5-mg group with an HR of 1.5 (95% CI, 0.7, 3.1). The MI rate was lower in the 0.5-mg group than in the other two groups. The observed treatment differences might result from the heterogeneity of the DME population.